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# POLIOMYELITIS

## I. EXPERIMENTAL AND THEORETICAL BASIS FOR SERUM THERAPY; A REVIEW

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CHICAGO

From the earliest experiences [1] with the use of serums in attempts to modify the course of acute poliomyelitis, controversial points have existed, and favor has shifted from one to another type of serum. The past few years have seen popular recognition of the use of serum taken from convalescents who have passed through a frank paralytic attack of the disease. Now that adequately controlled therapeutic experiments [2] are available in which equal numbers of patients in the early stage in the same epidemic remained without serum, additional doubt is being cast on the practical value of this and other types of serum. In part II the experiences of all the investigators who have attempted to treat poliomyelitis in the acute stage by serums and other measures are reviewed, and it is pointed out that when these previous reports are compared with observations on the average natural trend of the disease in the untreated preparalytic stage there is little evidence from a statistical point of view that the two groups differ in outcome. Thus, I believe that the large number of nonparalytic cases that occur in a group of preparalytic cases (43 to 95 per cent, table 1, pt. II) has been the factor that has favored the reports on the early treatment of this disease. Each

From the Department of Surgery, Division of Orthopedics, the University of Chicago.

1. (*a*) Peabody, F. W.: A Report of the Harvard Infantile Paralysis Commission on the Diagnosis and Treatment of Acute Cases of the Disease During 1916, New England J. Med. **176**:637, 1917. (*b*) Amoss, H. L., and Chesney, A. M.: A Report on the Serum Treatment of Twenty-Six Cases of Epidemic Poliomyelitis, J. Exper. Med. **25**:581, 1917. (*c*) Zingher, A.: The Diagnosis and Serum Treatment of Anterior Poliomyelitis, J. A. M. A. **68**:817 (March 17) 1917. (*d*) Rosenow, E. C.: The Production of an Antipoliomyelitis Serum in Horses, J. A. M. A. **69**:261 (July 28) 1917; The Treatment of Epidemic Poliomyelitis with Immune Horse Serum, ibid. **69**:1074 (Sept. 29) 1917; J. Infect. Dis. **22**:379, 1918.

2. (*a*) Kramer, S. D.; Aycock, W. L.; Solomon, C. I., and Thenebe, C. L.: Convalescent Serum Therapy in Preparalytic Poliomyelitis, New England J. Med. **206**:432, 1932. (*b*) Park, W. H.: Therapeutic Use of Antipoliomyelitis Serum in Preparalytic Cases of Poliomyelitis, J. A. M. A. **99**:1050 (Sept. 24) 1932.

serum that has been used therapeutically has been found by certain investigators to neutralize the virus of poliomyelitis in vitro. Almost without exception, every author who has reported on treatment with serum early in the acute stage has noted definite clinical evidence of arrest of the disease, especially in its acute manifestations. It is possible that enough clinical evidence alone can establish the use of serum, even with a lack of favorable statistical data.

There is a laboratory method of standardization for serums used in the treatment of diphtheria, tetanus, scarlet fever and certain other diseases that is a direct or proportionate measure of the expected therapeutic potency of the serum. It has long been assumed, but as yet never established, that the neutralizing potency of a serum against the virus of poliomyelitis is a measure of its therapeutic activity. That this is probably not true is indicated by the unfavorable results of therapeutic experiments in the pandemic of 1931,[2] when special care was taken to use only serum pools that had been shown to be active in vitro against the virus. As will be shown later, other attempts to arrive at a laboratory measure of therapeutic activity have been unsatisfactory.

In this review all the controversial evidence having a bearing on the use of serums in the treatment of acute poliomyelitis will be presented. This will include a review of recent conclusions concerning the etiology of the disease, since the causative organism has an important theoretical bearing on the choice of serums. There will also be presented the data obtained by various investigators by in vitro neutralization tests, as this activity is an evidence of an antiviral effect. Various methods of attempting an in vivo assay of the antiviral activity of serums will be reviewed. The practical results that have been obtained with various types of serums will be presented subsequently (pt. II, p. 1234 and tables 2 to 5).

## THE ETIOLOGIC AGENT OF POLIOMYELITIS

Until recently, the causative agent of this disease has been a subject of controversy. Landsteiner and Popper[3] were the first to offer a definite proof of the infectious nature of poliomyelitis when they succeeded in transmitting the disease to monkeys. Shortly thereafter, there appeared the confirmatory reports of many investigators[4] who were

3. Landsteiner, K., and Popper, E.: Uebertragung der Poliomyelitis acuta auf Affen: I, Ztschr. f. Immunitätsforsch. u. exper. Therap. **2**:377, 1909.

4. (*a*) Flexner, S., and Lewis, P. A.: The Transmission of Acute Poliomyelitis to Monkeys, J. A. M. A. **53**:2639 (Nov. 13) 1913; The Nature of the Virus of Epidemic Poliomyelitis, ibid. **53**:2095 (Dec. 18) 1909; (*b*) Experimental Epidemic Poliomyelitis in Monkeys, J. Exper. Med. **12**:227, 1910. (*c*) Leiner, C., and von Wiesner, R.: Experimentelle Untersuchungen über Poliomyelitis acuta anterior, Wien. klin. Wchnschr. **22**:1698, 1909. (*d*) Landsteiner, K., and Levaditi, C.: La transmission de la paralysie infantile aux singes, Compt. rend. Soc. de biol. **67**:592 and 787, 1909. (*e*) Römer, P. H.: Untersuchungen zur Aetiologie der epidemischen Kinderlähmung, München. med. Wchnschr. **56**:2505, 1909.

able to establish serial transmission of a filtrable infectious agent in monkeys. The earlier work on the etiology of this disease has been reviewed by Römer [5] and by Draper [6] and will not be repeated here. These reviews have been brought down to date by Fairbrother,[7] Long, Olitzky and Stewart,[8] Howitt [9] and Schultz [10] and in the recent survey sponsored by the International Committee for the Study of Infantile Paralysis.[11]

Rosenow and his co-workers,[12] Mathers [13] and Nuzum and Herzog [14] have been the chief proponents of the streptococcic etiology of this disease; they believed that the small micro-organisms, the so-called globoid bodies, that were cultivated from central nerve tissues by Flexner and Noguchi,[15] Flexner, Noguchi and Amoss [16] and Heist, Solis-Cohen and Kolmer [17] were but morphologic variants of the streptococci,

5. Römer, P. H.: (*a*) Epidemic Infantile Paralysis, New York, William Wood & Company, 1913; (*b*) Experimentelle Poliomyelitis, Ergebn. d. inn. Med. u. Kinderh. **8**:1, 1912.

6. Draper, G.: Acute Poliomyelitis, Philadelphia, P. Blakiston's Son & Co., 1917.

7. Fairbrother, R. W.: The Significance of Coccal Organisms in Experimental Poliomyelitis, J. Path. & Bact. **32**:435, 1929.

8. Long, P. H.; Olitzky, P. K., and Stewart, F. W.: The Rôle of Streptococci in Experimental Poliomyelitis of the Monkey, J. Exper. Med. **48**:431, 1928.

9. Howitt, B. F.: Poliomyelitis, California & West. Med. **33**:596, 1931.

10. Schultz, E. W.: Recent Advances in the Study of Poliomyelitis, J. Pediat. **1**:358, 1932.

11. International Committee for the Study of Infantile Paralysis, Poliomyelitis, Baltimore, Williams & Wilkins Company, 1932.

12. Rosenow, E. C., and Towne, E. B.: Bacteriological Observations in Experimental Poliomyelitis of Monkeys, J. M. Research **36**:175, 1917. Rosenow, E. C.; Towne, E. B., and Wheeler, G. W.: The Etiology of Epidemic Poliomelitis, J. A. M. A. **67**:1202 (Oct. 21) 1916. Rosenow, E. C., and Wheeler, G. W.: The Etiology of Epidemic Poliomyelitis, J. Infect. Dis. **22**:281, 1918.

13. Mathers, G.: Some Bacteriological Observations on Epidemic Poliomyelitis, J. A. M. A. **67**:1019 (Sept. 30) 1916; The Etiology of Acute Epidemic Poliomyelitis, J. Infect. Dis. **20**:113, 1917.

14. Nuzum, J. W., and Herzog, M.: Experimental Studies in the Etiology of Acute Epidemic Poliomyelitis, J. A. M. A. **67**:1205 (Oct. 21) 1916.

15. Flexner, S., and Noguchi, H.: Experiments on the Cultivation of the Virus of Poliomyelitis, J. A. M. A. **60**:362 (Feb. 1) 1913; Experiments on the Cultivation of the Microorganism Causing Epidemic Poliomyelitis, J. Exper. Med. **18**:461, 1913.

16. Flexner, S.; Noguchi, H., and Amoss, H. L.: Concerning Survival and Virulence of the Microorganism Cultivated from Poliomyelitis Tissues, J. Exper. Med. **21**:91, 1915.

17. Heist, G. D.; Solis-Cohen, M., and Kolmer, J. A.: Studies in Epidemic Poliomyelitis: I. The Isolation and Cultivation of the Globoid Bodies, J. Infect. Dis. **22**:169, 1918.

rendered small by prolonged anaerobic cultivation. There have always been certain theoretical considerations that have not permitted an unqualified acceptance of either the streptococci or the globoid bodies as visible forms of the virus or as the direct etiologic agent of the disease. The facts that the micrococcus or the streptococcus in its readily identifiable form produces lesions in rabbits and other animals [12] that have been repeatedly shown to be refractory to virus,[18] that the streptococcus is readily isolated from spinal fluid in both human [19] and experimental cases,[20] a menstruum which under ordinary circumstances is devoid of virus,[21] and that cocci closely resembling the alleged poliomyelitic organism may be isolated with considerable regularity from sources other than those closely related to the disease,[22] argue strongly against a belief that these organisms are etiologically related to the disease. The activity of the antistreptococcus serums against the virus of poliomyelitis will be discussed in a later section of this article. That the pathologic changes produced by intracerebral inoculation of the globoid bodies are not typical of poliomyelitis,[17] that many authors [23] have failed to note any pathogenic property in the globoid bodies and that these organisms are poor antigens, failing to produce serums that have demonstrable neutralizing effect on the virus, are facts that cast grave doubt on the active rôle of the globoid bodies in the pathogenesis of poliomyelitis.

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18. Harmon, P. H.; Shaughnessy, H. J., and Gordon, F. B.: The Effect upon Animals of Inoculation with Virus of Poliomyelitis: I. Rabbits, J. Prev. Med. **4**:59, 1930; II. Dogs, Cats, Guinea Pigs, Mice and Other Animals, ibid. **4**:89, 1930.

19. Nuzum, J. W.: Bacteriologic Findings in Cerebrospinal Fluid in Poliomyelitis, J. A. M. A. **67**:1437 (Nov. 11) 1916.

20. Rosenow, E. C.: Streptococci in Spinal Fluid in Acute Epidemic Poliomyelitis, J. A. M. A. **91**:1594 (Nov. 24) 1928; Streptococci in the Lesions of Experimental Poliomyelitis in Monkeys, Proc. Soc. Exper. Biol. & Med. **27**:444, 1930.

21. (*a*) Flexner, S., and Clark, P. F.: Epidemic Poliomyelitis: XI, J. A. M. A. **57**:1685 (Nov. 18) 1911. (*b*) Clark, P. F., Amoss, H. L.: Intraspinous Infection in Experimental Poliomyelitis, J. Exper. Med. **19**:217, 1914. (*c*) Flexner, S., and Amoss, H. L.: Penetration of the Virus of Poliomyelitis from the Blood into the Cerebrospinal Fluid, ibid. **19**:411, 1914. (*d*) Abramson, H. L.: Does the Spinal Fluid from Human Poliomyelitis Contain the Specific Infective Agent? J. A. M. A. **68**:546 (Feb. 17) 1917.

22. Tsen, E. T. H.: The Etiology of Epidemic Poliomyelitis, J. Exper. Med. **28**:269, 1918. Footnotes 7 and 8.

23. Smillie, W. G.: Cultivation Experiments on the Globoid Bodies of Poliomyelitis, J. Exper. Med. **27**:319, 1918. Krauspe: Uebertragung der akuten Poliomyelitis des Menschen auf kleinere Laboratoriumstiere, Verhandl. d. deutsch. path. Gesellsch. **23**:442, 1928.

Fairbrother,[7] Long, Olitzky and Stewart,[8] Cooper,[24] Rosenow [20] and Olitzky, Rhoads and Long [25] recently reexamined the whole question of the relationship of coccal organisms to the disease. Fairbrother examined the central nervous system and blood of animals with the experimental disease by bacteriologic methods, together with similar materials derived from normal monkeys and animals with other diseases. The experimental monkeys were killed in the initial stage of the disease, when moribund from extensive paralysis, and a few were examined after death from the disease. Streptococci, both of the variety producing greenish discoloration on blood agar and of the inert variety, were isolated from certain animals in all these groups, but with greater regularity from the animals with poliomyelitis. In the latter groups, cocci were isolated more frequently when the animals were moribund than during the early stages of the disease. The results of morphologic and cultural examinations, while showing certain irregularities among the whole group, were as nearly identical as could be expected among such a notably variable group of micro-organisms. These properties agreed well with those of organisms isolated from the nasopharynx of normal animals and with those of the diplostreptococcus of Rosenow. Fairbrother's conclusions were that the coccal organisms present in poliomyelitis are "members of the group of air micrococci and occur as air-borne contaminants, although under certain circumstances they may be found as terminal invading organisms, arising probably from the naso-pharynx." Long, Olitzky and Stewart found that by making cultures in places where the expectancy of air-borne contamination varied, cultures of streptococci were obtained from poliomyelitic tissues in direct ratio to the possibility of such contamination. In a room designed for work on tissue culture where extraordinary precautions against contamination by air could be taken, no cultures of streptococci were obtained. Long, Olitzky and Stewart obtained similar organisms from nonpoliomyelitic tissues. By fermentation tests and agglutination reactions they showed the relative dissimilarity of many of the organisms, since strains from the air and from other nonpoliomyelitic sources were often grouped with cocci forwarded to them by Rosenow for study and with the organisms which they had isolated from poliomyelitic tissues. They concluded: "The results of the experiments . . . point to another source of the streptococci. They occur as contaminants which are introduced into the cultures during the process of grinding the tissues."

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24. Cooper, M. L.: The Cause of Poliomyelitis, Am. J. Dis. Child. **42**:702 (Sept.) 1931.

25. Olitzky, P. K.; Rhoads, C. P., and Long, P. H.: Relation of Streptococci to Spinal Fluid in Experimental Poliomyelitis, J. A. M. A. **92**:1725 (May 25) 1929.

Since the bacteriologic observations on an experimental disease in animals do not necessarily agree with those on the naturally occurring disease of man, as Reith [26] has shown that bacteria can be isolated with considerable regularity from fresh animal tissues, the recent studies that have been made on poliomyelitis in man are of importance. In studying several recent epidemics Rosenow [20] has been able to isolate a green-producing diplostreptococcus from the spinal fluid in a specially devised yeast medium. Control cultures made from spinal fluids removed from patients with diseases not involving the nervous system and from those with other diseases of the central nervous system failed to yield these organisms either in smear or in culture. These streptococci failed to reproduce the experimental disease in monkeys, as has always been the case with these organisms; however, they did produce a poliomyelitis-like disease in rabbits. Monkeys are the only known animals in which the virus will reproduce the disease experimentally, while rabbits have been repeatedly and conclusively shown to be refractory to inoculation with virus. This discrepancy is explained by Rosenow as a change in virulence in respect to animal hosts. That this is a valid explanation may be questioned, since, if there were a change in the virulence of the organisms, it should be possible to find certain strains with variable virulence for these two hosts. Such theoretical strains have never been observed. That there are variations in affinity for a host among different strains of the virus is indicated by the difficulty with which infectious material from certain epidemics can be established by passage through monkeys.[27] Olitzky, Rhoads and Long [25] attempted to repeat the recent work of Rosenow with the special yeast medium and were unable to obtain viable cultures, although film preparations from the yeast medium showed numerous streptococci. These organisms were believed to be dead, having their original derivation from the yeast used in the preparation of the medium. Rosenow [20] stained sections of the central nervous system obtained from 60 experimental monkeys with poliomyelitis and from 60 animals that either were normal or had succumbed to some other disease. In the sections from animals with poliomyelitis, diplostreptococci could be seen in large numbers adjacent to the lesions, while in similar sections from the control animals, no organisms could be seen. Recently

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26. Reith, A. F.: Bacteria in Muscular Tissues and Blood of Apparently Normal Animals, J. Bact. **12**:367, 1926.

27. (*a*) Jonesco-Mihaiesti, C.; Tupa, A., and Wisner, B.: Sur un virus de poliomyélite s'atténuant au cours des passages, Compt. rend. Soc. de biol. **99**:12, 1928; Sur le virus poliomyélitique de Roumanie en 1928, ibid. **100**:919, 1929. (*b*) Paul, J. R., and Trask, J. D.: The Detection of Poliomyelitis Virus in So-Called Abortive Types of the Disease, J. Exper. Med. **56**:319, 1932; (*c*) A Comparative Study of Recently Isolated Human Strains and a Passage Strain of Poliomyelitis Virus, J. Exper. Med. **58**:513, 1933.

Rosenow [28] has found that streptococci from poliomyelitic sources have a characteristic cataphoretic velocity. Convalescent serum from both man and monkeys was found to have a specific slowing effect on the electrophoretic velocity of the streptococci of poliomyelitis. Suggestive as this evidence is, there still remains the fact that these streptococci have not reproduced typical lesions in a susceptible species. Cooper [24] recently cultivated streptococci with a certain amount of consistency (65 per cent of cases) from the spinal fluid of patients with the disease, but the use of rabbits in his experiments militates against an acceptance of his views.

Harmon, Shaughnessy and Gordon [29] were able to confirm the results obtained by Fairbrother and Long, Olitzky and Stewart. The streptococcus strains that they were able to isolate were without demonstrable effect, even when introduced repeatedly in large numbers into the cranial cavity of monkeys. When these animals were subsequently tested for resistance to the virus, all became typically and completely paralyzed. Rosenow [30] vaccinated monkeys with the streptococcus, producing a certain amount of immunity even when measured by the severe intracerebral introduction of a test dose of virus. A comparison of the resistance in monkeys inoculated with streptococci to that of untreated control monkeys, while significant as given by Rosenow, gave merely statistical differences; the results were not absolute.

Richardson and Mellon [31] cultivated by the Hauduroy transplant method similar green-producing streptococci from Berkefeld N filtrates of broth cultures of the Rosenow streptococcus and from emulsions of the brain of animals previously inoculated intracerebrally with this same organism. These experiments demonstrate that the streptococcus of Rosenow is filtrable. Richardson and Mellon were reasonably certain that the streptococcus removed in this way from the broth and brain filtrates was the same organism as the one with which they started, but they did not believe this to be the vital issue. They contended that the important point was the question of the identity of this filtrable streptococcic form with the virus of poliomyelitis. Since poliomyelitis did not develop in monkeys which had received intracerebral injections of these

28. Rosenow, E. C.: A Specific Reaction of Convalescent Serum on the Streptococcus Isolated in Studies of Poliomyelitis, J. Immunol. **23**:455, 1932.

29. Harmon, P. H.; Shaughnessy, H. J., and Gordon, F. B.: Unpublished experiments.

30. Rosenow, E. C.: Poliomyelitis Antistreptococcus Serum: Further Studies on the Bacteriology and Serum Treatment of Poliomyelitis, J. A. M. A. **94**:777 (March 15) 1930.

31. Richardson, R. D., and Mellon, R. R.: Experiments on the Filterability of the Rosenow Streptococcus of Anterior Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **29**:451, 1932.

filtrates of the streptococcus, Richardson and Mellon believed that the filtrable streptococcic forms had been conclusively shown not to be identical with the virus; they were inclined to compromise on views as to the etiology of poliomyelitis: "As a result of the altered conditions brought about in the host by the virus, there is dissociated in vitro a form of streptococcus which reacts specifically with the host."

Long and Olitzky [32] reexamined the survival of streptococci of poliomyelitis in glycerin, arguing that if these organisms were identical with or related to the virus, they should have a comparable resistance to this agent. Rhoads [33] had already shown that the virus survived in brain tissue preserved in glycerin for at least eight years. Long and Olitzky found that the streptococci did not have a comparable longevity, as cultural transplants were obtained from brain tissue that had been originally inoculated with streptococci only between eighty-two and three hundred and three days after the original preservation of these brains in glycerin.

Eberson [34] recently reported the successful cultivation of a minute organism with which he had been able to reproduce the disease by reinoculation of monkeys with cultures remote from the original. In this work a heat-sterilized medium was used in order to escape the numerous objections to the fresh tissue and ascitic fluid medium of Smith and Noguchi that has been used for the cultivation of the globoid bodies. The possible relationship of this organism to the globoid bodies and to filtrable forms of the streptococci was not entertained by Eberson. In the amplified reports by Eberson and Mossman [35] abundant evidence is offered that the virus has multiplied in vitro. Indeed, all of Koch's postulates seem to have been fulfilled by these authors, and, in addition, evidence is presented [36] that antiviral immunity is conferred by inoculation of the minute organism. Long, Olitzky and Rhoads [37] have like-

32. Long, P. H., and Olitzky, P. K.: Comparison of Resistance of Streptococci and of Poliomyelitis Virus in Glycerol, Proc. Soc. Exper. Biol. & Med. **26:** 337, 1929.

33. Rhoads, C. P.: Survival of the Virus of Poliomyelitis for Eight Years in Glycerol, J. Exper. Med. **49:**701, 1929.

34. Eberson, F.: Etiology of Poliomyelitis: Cultivation of an Organism from Poliomyelitic Tissue and Transmission of the Disease in Monkeys, Proc. Soc. Exper. Biol. & Med. **29:**477, 1932; Science **75:**519, 1932.

35. Eberson, F., and Mossman, W. G.: Studies on the Etiology of Poliomyelitis, J. Lab. & Clin. Med. **18:**565, 1933; Procedures in the Isolation and Cultivation of an Organism from Berkefeld N Filtrates of Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **30:**92, 1932.

36. Eberson, F.: Experimental Study of an Antipoliomyelitic Serum from Monkeys Artificially Immunized with an Organism Cultivated from Poliomyelitis Nervous Tissue, J. Immunol. **24:**433, 1933.

37. Long, P. H.; Olitzky, P. K., and Rhoads, C. P.: Survival and Multiplication of the Virus of Poliomyelitis in Vitro, J. Exper. Med. **52:**361, 1930.

wise obtained evidence of the multiplication of the virus in vitro but Schultz [10] has been unable to confirm the findings of Eberson.

Long, Olitzky and Rhoads [37] attempted to repeat the previous work of Flexner and Noguchi [15] and of Flexner, Noguchi and Amoss [16] who first cultivated the globoid bodies and stated that they had successfully infected monkeys with their cultures. A large number of cultures of monkey brain obtained from typical experimental animals were made in Smith-Noguchi medium, which, as stated, contains fresh ascitic fluid and fresh sterile rabbit kidney. Small organisms resembling the globoid bodies of Flexner and Noguchi were seen in but thirty-six of three hundred and fifteen tubes. Long, Olitzky and Rhoads stated:

> A study of subplants from these minute morphological particles did not convince us that we had in hand actual cultures of the globoid bodies, or indeed of any living microorganism. Nevertheless, when washed sediments from subplants of one of the strains were inoculated into monkeys, the clinical signs and the pathological effects characteristic of experimental poliomyelitis could be induced.

They were inclined to believe that they had merely cultivated the poliomyelitis virus in vitro in the presence of a culture of living tissue cells rather than a particulate micro-organism. In this connection, the comment of Rivers,[38] "I do not believe that globoid bodies represent the etiological agent of poliomyelitis," is of importance.

Many recent studies on the purification and concentration of the virus of poliomyelitis have appeared; these demonstrate the astonishing resistance of the organism to certain chemicals. Preparations having an exceedingly small infective dose have been obtained. Clark, Schindler and Roberts [39] employed the method of in vacuo distillation of virus mixtures by which they obtained a saturated solution of sodium chloride containing the virus in advanced concentration. The virus was found to retain its infectivity for more than four months in this menstruum. They have made many unsuccessful attempts to cultivate an organism from these concentrated preparations of virus. In contrast, they found that streptococci isolated from cases of poliomyelitis did not survive more than thirty-five days in saturated solutions of sodium chloride. Rhoads [40] has shown that the virus of poliomyelitis can be adsorbed on particles of colloidal aluminum hydroxide at slightly acid $p_H$ values. Using this fact

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38. Rivers, T. M., personal communication to Park, W. H., quoted by Harrington, H., in International Committee for the Study of Infantile Paralysis,[11] p. 44.

39. (*a*) Clark, P. F.; Schindler, J., and Roberts, D. J.: Some Properties of Poliomyelitis Virus, J. Bact. **20**:213, 1930. (*b*) Clark, P. F.; Roberts, D. J., and Preston, W. S.: Passage of Poliomyelitis Virus Through the Intestinal Tract, J. Prev. Med. **6**:47, 1932.

40. Rhoads, C. P.: Immunization with Mixtures of Poliomyelitis Virus and Aluminum Hydroxide, J. Exper. Med. **53**:399, 1931.

and the general methods employed by Willstätter and his associates for the purification of enzymes, Sabin [41] and Harrison and Hudson [42] eliminated a large part of the organic constituents of the original filtrates or suspensions of virus. Clark, Ainsworth and Kindschl [43] have recently described a method of concentration of the virus by ultrafiltration through soluble membranes of gun cotton that was successful in eliminating a large quantity of extraneous material from virus filtrates. Some of the preparations have been so potent that in certain experiments small quantities (0.0003 cc.) produced poliomyelitis in five days in monkeys. Streptococci could not be isolated from any of these purified preparations after passage through Berkefeld N filters, although the infective property was adequately retained. Such observations indicate that a method is available for studying the fundamental and biologic properties of this virus in the absence of a large amount of soluble brain tissue, which heretofore had been present in all the preparations used for such studies.

### ANTIVIRAL ACTION OF SERUMS

*Nature of the In Vitro Test for Neutralization of Virus.*—Soon after the discovery of the virus of poliomyelitis, Levaditi and Landsteiner [44] showed that the serum of monkeys convalescent from the experimental disease contained a substance that prevented infection when serum and virus were incubated in vitro. Several confirmatory reports [45] of independent investigators followed in rapid succession. Netter and Levaditi [46] and Flexner and Lewis [45c] demonstrated that

41. Sabin, A. B.: Purification of Poliomyelitis Virus by Adsorption and Elution, Proc. Soc. Exper. Biol. & Med. **29**:59, 1931; J. Exper. Med. **56**:307, 1932.

42. Harrison, J. W., and Hudson, N. P.: Personal communication to the author.

43. Clark, P. F.; Ainsworth, R. C., and Kindschl, L. G.: Concentration of Poliomyelitis Virus by Ultrafiltration, Proc. Soc. Exper. Biol. & Med. **31**:255, 1933.

44. Levaditi, C., and Landsteiner, K.: La poliomyélite expérimentale (cinquième note), Compt. rend. Soc. de biol. **68**:311, 1910. Landsteiner, K., and Levaditi, C.: Étude expérimentale de la poliomyélite aiguë, Ann. Inst. Pasteur **24**:833, 1910.

45. (*a*) Leiner, C., and von Wiesner, R.: Experimentelle Untersuchungen über Poliomyelitis acuta anterior, Wien. klin. Wchnschr. **23**:323, 1910. (*b*) Römer, P. H., and Joseph, K.: Spezifisch wirksames Serum gegen das Virus der epidemischen Kinderlähmung, München. med. Wchnschr. **57**:568, 1910. (*c*) Flexner, S., and Lewis, P. A.: Experimental Poliomyelitis in Monkeys: Seventh Note: Active Immunization and Passive Serum Protection, J. A. M. A. **54**:1780 (May 28) 1910.

46. Netter, A., and Levaditi, C.: Action microbicide exercée par le sérum des malades atteints de paralysis infantile sur le virus de la poliomyélite aiguë, Compt. rend. Soc. de biol. **68**:617, 1910.

serum from persons who had recovered from a paralytic attack of the disease had similar neutralizing substances in their blood stream. It was then assumed that these neutralizing substances would be virucidal in vivo. Thus, convalescent serum was soon used for treatment of the disease in man (pp. 1217 and 1218).

When attempts were made to protect monkeys passively during the period of incubation by the serum of convalescent monkeys, it was found that in order to effect protection in an appreciable number of animals serum had to be given either before or at the time the virus was inoculated. Both Leiner and von Wiesner [45a] and Levaditi and Landsteiner [44] were unable to protect monkeys when the serum of convalescent monkeys was given intraperitoneally at the same time that virus was inoculated intracerebrally. This failure was not due to inadequate doses of serum, since in some experiments reported by these authors the administration of serum by the same route was continued for a few days into the period of incubation with the same result. Although Flexner and Lewis [45c] were in some measure successful in protecting monkeys against the infection by virus given twenty-four hours before protective inoculations were begun, they also noted certain irregularities. They stated definitely that the protection was not absolute, but that the inoculations of virus could "not be given in excess of a given dose." They also noted that intraperitoneal injections of serum would block infection by way of the nasal mucosa, even when the series of protective inoculations were delayed until twenty-four hours after the intranasal instillation of the test dose of virus.

These early attempts to demonstrate the in vivo action of neutralizing substances may be criticized on several grounds. That the nature of the in vitro neutralization reaction was not even well understood is evidenced by work showing that the test is a serologic reaction in which the virus is only rendered ineffective. Similarly to the toxin-antitoxin reaction, the neutralization reaction can be reversed under certain circumstances. That the reaction is not a direct virucidal phenomenon and is not similar to bactericidal reactions is thus demonstrated. Objections have also been raised by certain authors that the in vitro neutralization test may not be a specific reaction. However, enough evidence has been accumulated to disprove this last contention adequately (p. 1224). A lack of basic data on the relative susceptibility of animals to various routes of inoculation by the virus renders invalid the early experiments in which the virus was given by routes other than the intracerebral method, since they are all based on the erroneous assumption that other routes of inoculation invariably lead to paralysis in experimental monkeys.

That virus can be recovered from neutral mixtures that fail to infect experimental monkeys has been shown by Olitzky, Rhoads and Long,[47] Levaditi and Lépine[48] and by Schultz, Gebhardt and Bullock.[49] The former two groups of authors were able to recover virus at the anode in cataphoresis of neutral serum-virus mixtures. Schultz, Gebhardt and Bullock believe that the antiviral antibodies in convalescent serum resemble antitoxic antibodies, since a neutral serum-virus mixture can be rendered infective by dilution with isotonic saline solution. When diluted serum is used in the neutralization test, an appreciable length of time is required to bring the reaction to completion.

The occurrence of neutralizing bodies in the blood serum of adults in regions where poliomyelitis is either rare (Puerto Rico, Soule and McKinley;[50] Greenland and China, Jungeblut;[51] Liberia and China, Hudson and Lenette[52]) or absent (Virgin Islands, Shaughnessy, Harmon and Gordon[53]) has been adduced by some as evidence that the acquisition of these properties is a nonspecific maturation phenomenon. That there is probably more evidence that these substances represent specific acquired immunity due to contact with the virus will be pointed out later (p. 1225). Since the phenomena of acquired immunity are manifested in different ways in susceptible and in nonsusceptible species, the situation is somewhat clouded in man, since his is the only species known to be naturally susceptible to the disease. The invalidity of application to man of the recent unsuccessful attempts to produce immune substances in monkeys by the repeated intranasal instillation of

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47. Olitzky, P. K.; Rhoads, C. P., and Long, P. H.: Effect of Cataphoresis on Poliomyelitis Virus, J. Exper. Med. **50**:273, 1929.

48. Levaditi, C., and Lépine, P.: Determination by Cataphoresis of Poliomyelitis Virus in the Spinal Cord of Monkeys with Chronic Lesions, Compt. rend. Soc. de biol. **106**:34, 1931.

49. Schultz, E. W.; Gebhardt, L. P., and Bullock, L. T.: Studies on the Nature of the Viricidal Antibodies in Antipoliomyelitis Serum, Proc. Soc. Exper. Biol. & Med. **28**:28, 1930; J. Immunol. **21**:171, 1931.

50. Soule, M. H., and McKinley, E. B.: Neutralization of the Virus of Poliomyelitis with Serum of Healthy Porto Ricans, Proc. Soc. Exper. Biol. & Med. **29**:168, 1931.

51. Jungeblut, C. W.: The Power of Normal Human Sera to Inactivate the Virus of Poliomyelitis in Its Relation to Blood Grouping and Exposure, J. Immunol. **24**:157, 1933. Jungeblut, C. W., and Smith, L. W.: Blood Grouping in Poliomyelitis and the Neutralizing Property of Convalescent Serum, ibid. **23**:35, 1932.

52. Hudson, N. P., and Lenette, E. H.: Neutralization of Poliomyelitis Virus by the Serum of Liberian Negroes, Proc. Soc. Exper. Biol. & Med. **29**:1090, 1932. Lenette, E. H., and Hudson, N. P.: Neutralization of Poliomyelitis Virus by the Serum of Native Chinese of Peiping, ibid. **30**:449, 1933.

53. Shaughnessy, H. J.; Harmon, P. H., and Gordon, F. B.: The Neutralization of Poliomyelitis Virus by Human Serum, J. Prev. Med. **4**:463, 1930.

subinfective doses of virus as reported by Jungeblut and Hazen [54] and Flexner [55] rests on this very point. The incidence of neutralizing substances in the blood of rhesus monkeys, a species that is only artificially susceptible to the disease, demonstrates that only animals which have been known to have had contact with the virus either by a paralytic attack of the disease [56] or by artificial active immunization [57] have neutralizing substances. All the investigators agree that normal monkeys do not have neutralizing substances in their blood serum.[58] The only apparent exception to the latter fact has been reported by Jungeblut and Hazen,[59] who mention the presence of neutralizing substances in the blood of normal adult female rhesus monkeys in the postmenstrual period. Such an observation has a bearing on the endocrine fluctuations in relation to purely immunologic phenomena, a field whose exploitation is just beginning. Since these authors found only 2 of 12 such monkeys had neutralizing substances under these circumstances, since they failed to define such fluctuations in any particular phase of the menstrual

54. Jungeblut, C. W., and Hazen, E. L.: Failure to Immunize the Monkey Against Poliomyelitis by Prolonged Nasopharyngeal Spraying with Live Virus, Proc. Soc. Exper. Biol. & Med. **28**:1004, 1931.

55. Flexner, S.: Immunity to Human and Passage Poliomyelitis, J. A. M. A. **99**:1244, 1932.

56. Footnotes 40 and 41.

57. (*a*) Aycock, W. L., and Kagan, J. R.: Experimental Immunization in Poliomyelitis, J. Immunol. **14**:85, 1927. (*b*) Rhoads, C. P.: Intradermal Immunization of Monkeys with One Set of Injections of Poliomyelitis Virus, J. Exper. Med. **51**:1, 1930; Immunity Following the Injection of Monkeys with Mixtures of Poliomyelitis Virus and Convalescent Human Serum, ibid. **53**:115, 1931; Immunization with Mixtures of Poliomyelitis Virus and Aluminum Hydroxide, ibid. **53**: 399, 1931. (*c*) Stewart, F. W., and Rhoads, C. P.: Intradermal versus Subcutaneous Immunization of Monkeys Against Poliomyelitis, ibid. **49**:959, 1929. (*d*) Jungeblut, C. W., and Hazen, E. L.: A Comparison of the Efficacy of Different Methods of Active Immunization in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **28**:10, 1930. (*e*) Goldbloom, A.; Brodie, M., and Moffatt, W.: Active Immunization Against Poliomyelitis in Monkeys, Am. J. Dis. Child. **40**:923 (Oct.) 1930; J. Exper. Med. **53**:885, 1931. (*f*) Brebner, W. B.: The Immunization of Monkeys Against the Virus of Poliomyelitis, Am. J. Path. **7**:546, 1931. (*g*) Kramer, S. D., and Schaeffer, M.: Experimental Poliomyelitis. Active Immunization with Neutralized Mixtures of Virus and Serum, Proc. Soc. Exper. Biol. & Med. **31**:409, 1934.

58. (*a*) Pettit, A.: Utilization du singe pour la production du sérum poliomyélitique, Bull. Acad. de méd., Paris **102**:312, 1929. (*b*) Aycock, W. L., and Kramer, S. D.: Immunity to Poliomyelitis in Normal Individuals in Urban and Rural Communities as Indicated by the Neutralization Test, J. Prev. Med. **4**:189, 1930. (*c*) Footnote 4b. (*d*) Footnote 53.

59. Jungeblut, C. W., and Hazen, E. L.: On the Property of Certain Normal Animal Sera to Neutralize the Virus of Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **29**:879, 1932.

cycle in women [60] and since no confirmation of their work has appeared it is logical to assume that the 2 animals in which positive neutralization was obtained represent "missed cases" of experimental poliomyelitis as demonstrated by the previous work of Harmon, Shaughnessy and Gordon.[61]

That constitutional factors may have a bearing on the acquisition of neutralizing substances against the virus of poliomyelitis has just been brought out by other recent work, although these facts do not bring evidence that the reaction is not specific. Jungeblut and Engle [62] observed the acquisition of a small titer of neutralizing substance in certain monkeys rendered artificially mature by injections of anterior pituitary hormone or by implants of pituitary gland. Such experiments suggest that the postadolescent endocrine balance is a factor in the acquisition of a neutralizing substance. In putting to test previous work on the incidence of blood groups among the victims of naturally occurring poliomyelitis,[63] Jungeblut and Smith [64] found that persons of group B (Moss III) were practically absent from a group of 578 patients in the New York City pandemic of 1931, thus suggesting a more rapid and complete acquisition of natural immunity in persons of this blood group. In order further to test this implied indication they performed neutralization tests on the serum of "normal" persons of the three uncomplicated groups (O, A and B), with the result that a greater percentage of group B than of the other two groups were found to neutralize the virus. A quantitative titration of the pooled serums from each group showed that the titer of the B pool was many times greater than that of pools of the other two groups. According to Jungeblut,

60. (*a*) Jungeblut, C. W., and Engle, E. T.: The Influence of Pregnancy and Menstruation on the Power of Normal Human Serum to Inactivate Poliomyelitis Virus, J. Immunol. **24**:267, 1933; (*b*) An Investigation into the Significance of Hormonal Factors in Experimental Poliomyelitis, J. Exper. Med. **59**:43, 1934; (*c*) Resistance to Poliomyelitis: The Relative Importance of Physiologic and Immunologic Factors, J. A. M. A. **99**:2091 (Dec. 17) 1932.

61. Harmon, P. H.; Shaughnessy, H. J., and Gordon, F. B.: Missed Infections, Abortive and Relapsing Cases of Experimental Poliomyelitis, J. Prev. Med. **5**:139, 1931.

62. (*a*) Jungeblut, C. W., and Engle, E. T.: Susceptibility Problems in Poliomyelitis, Am. J. Dis. Child. **43**:523 (Feb.) 1932. (*b*) Footnote 60b and c.

63. (*a*) Marinesco, G.; Manicatide, M., and Draganescu, S.: L'epidémie de paralysie infantine qui a sévi en Roumanie pendant l'année 1927, Ann. Inst. Pasteur **43**:223, 1929. (*b*) Grooten, O., and Kossovitch, C.: Sur les groupes sanguins chez les enfants poliomyélitiques, Compt. rend. Soc. de biol. **105**:428, 1930. (*c*) Foà, A.: Sui gruppi sanguigni nei bambini poliomyelitici, Pediatria d. med. prat. **6**:178, 1931.

64. Jungeblut, C. W., and Smith, L. W.: Blood Grouping in Poliomyelitis. Its Relation to Susceptibility and the Neutralizing Property of Convalescent Serum, J. Immunol. **23**:35, 1932.

similar titrations on convalescent serum of these three blood groups [51] demonstrated that the constitutional factor of blood grouping was as important as a typical paralytic attack of poliomyelitis. If these observations can be confirmed when extended, they will offer a clearcut constitutionally linked factor of resistance.

*Technic.*—The technic that has been employed in in vitro neutralization tests has varied from time to time with the same authors and among different groups of investigators. Thus, comparisons of results obtained by different groups are not justified except in a general way, even when recent studies are reviewed in which attempts have been made to estimate neutralizing substance comparatively. In this study, methods that have been used with various types of serums will be presented indiscriminately, since methods rather than results are to be followed. The early methods used in performing the neutralization test can only be mentioned, as such important factors as the numbers of paralyzing doses of virus used, the size of the inoculum, the proportions of virus and serum and the method of preparation of the virus varied within wide limits. Undoubtedly contradictions in the hands of different investigators can, in part, be explained by the lack of a uniform technic. When this test was employed in earlier years,[65] authors were content with merely mixing a small quantity (from 0.5 to 1.5 cc.) of undiluted serum with an identical or comparable quantity of "virus suspension." This mixture was incubated from two to four hours at 37 C., held overnight at ice-chest temperature (from 4 to 8 C.) and then inoculated into monkeys by the reliable intracerebral method. These conditions of time and temperature used prior to inoculation have become the only universally accepted part of the technic of this reaction. A semistandardized technic was evolved by the workers at the Rockefeller Institute who utilized a small quantity (0.1 or 0.01 cc.) of a virus filtrate (Berkefeld) of moderate potency with from 9 to 99 volumes of the serum to be tested. While it is certain that multiples of a fatal dose of virus were employed in these experiments, an overwhelming advantage is given to serum. Notwithstanding these specious criticisms, the results obtained by this group of workers have been remarkably consistent, as by this method Rhoads and his associates [57b, c] have demonstrated neutralizing substances in the blood of artificially immunized monkeys. Other authors who employed this test during a current period utilized a somewhat different relative proportion of serum and virus. Nuzum [66] used virus suspensions clarified by filtration through many thicknesses of filter paper, as well as Berkefeld filtrates of virus suspensions, but he was careful never to have overwhelming quantities of virus or of

65. Footnotes 45 and 46.

66. Nuzum, J. W.: A Study of the Neutralizing Properties of Antipoliomyelitic Horse Serum, J. Infect. Dis. **23**:301, 1918.

serum present in an in vitro mixture. Rosenow [67] employed the same technic that Nuzum used, likewise giving consideration to suitable proportions of serum and virus.

It should be emphasized that the potency of a strain of virus in terms of the minimal infective dose used in many neutralization tests has not been stated in the corresponding reports, nothwithstanding the well recognized fact that different strains vary in infective potency. For instance, it required from 1 to 2 cc. of a 5 per cent crude emulsion of the "M. A." virus, now a weak strain, to infect an animal intracerebrally when Harmon, Shaughnessy and Gordon [29] had an opportunity to examine a specimen of this virus, forwarded to them by Dr. Flexner in 1928. In their hands, the Aycock strain has proved to be a virus of moderate but consistent virulence, requiring from 0.25 to 0.4 cc. of a 5 per cent emulsion to infect an animal intracerebrally. The virus ("P. M. V." or "Fl. M." strain) recently used by Rhoads and others, which these authors had an opportunity to utilize after Dr. Rhoads forwarded them a specimen in 1929, has been of extreme virulence, often infecting monkeys in quantities as small as from 0.01 to 0.05 cc. of a 5 per cent emulsion of spinal cord tissue. Thus it can be seen that the multiples of minimal infective doses carried in a "standard dose" of 0.1 or 0.5 cc. of virus emulsion or filtrate vary greatly depending on the strain of virus.

Recently, Stewart and Hazelbauer [68] have reduced the preponderating advantage held by a large relative volume of serum and have employed virus filtrate with the serum to be tested in a proportion of 1 : 3 in a total volume of 1.2 cc. Such a method unquestionably allows less advantage to the serum. Other workers in the same laboratory (Rhoads, and Stewart and Rhoads [69]) still use overwhelming amounts of 9 and 99 parts of serum to 1 of virus, when attempting to detect neutralizing substances that may be present in only small concentrations, as in the blood stream of animals that have been actively immunized by artificial methods. In other experiments, the latter authors elect to mix serum and virus with less preponderating portions of serum when they do not suspect that the serum to be tested will have to be given the advantage of overwhelming volume to demonstrate neutralizing substances. Other authors have adopted a more rational and standardized technic rather than these arbitrary and variable methods.

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67. Rosenow, E. C.: Treatment of Acute Poliomyelitis with Immune Horse Serum: Further Studies, J. A. M. A. **71**:433 (Aug. 8) 1918. Footnote 30.

68. Stewart, F. W., and Hazelbauer, P.: Virus Neutralization Experiments with Rosenow's and Pettit's Antipoliomyelitic Sera, J. Exper. Med. **48**:449, 1928.

69. (*a*) Rhoads, C. P.: Experimental Study of a Horse Antipoliomyelitis Serum, J. Exper. Med. **53**:123, 1931. Footnote 57c.

Fairbrother [70] was the first to attempt a titration of serum against a known amount of virus, obtaining in this way comparative values that represented a progressive acquisition of antiviral properties in a horse that was being immunized with virus suspensions. He preferred a rather severe test of serum against a fixed amount of 100 infecting doses of virus. He described his modifications as follows:

> The strain employed in this work (viz. "Fl. M.") [71] was one of great potency. . . . It will be observed that the minimal infecting dose is roughly between 0.0005 cc. and 0.003 cc.; i. e., the dose employed throughout in the tests is at least 100 times the minimal infecting dose. In order to titrate the various samples of serum, the amount of virus emulsion was kept constant, while the quantity of serum was varied; 0.4 cc. of a 5 per cent virus emulsion was mixed with 0.6 or 0.4 cc. of the different samples of serum. . . . A further attempt to titrate the various samples of serum was made. The virus amount in all cases was 0.6 cc., while the serum was added in much smaller amounts, 0.1 and 0.2 cc.

Notwithstanding a few irregularities, Fairbrother's results demonstrated definitely that when the test dose of virus was increased from 0.4 to 0.6 cc. (from 130 to 200 minimal infecting doses) more serum was needed to neutralize the advanced dosage, implying quantitative relations between the two agents. In a test of human convalescent serum this author noted: "When the proportion of serum to virus was greater than or equal to unity, protection occurred, but when the virus amount exceeded that of the serum, infection took place after a lengthened incubation period." Such phenomena had been repeatedly observed in the literature, but Fairbrother seems to be the first to have taken cognizance of the importance of the quantitative relations between the two variables, virus and serum.

Working independently, Shaughnessy, Harmon and Gordon [53] evolved a quantitative method of estimating the content of neutralizing substances in serum that is more satisfactory as a moderately exacting test:

> Three dilutions of each serum were tested against a constant amount of the virus preparation. The virus preparation and the serum dilutions just described were mixed in quantities of 1.5 cubic centimeters each, placed in the incubator at 37° C. for two hours and then in the ice box for eighteen to twenty hours. The mixtures were injected intracerebrally in two cubic centimeter quantities into healthy unused monkeys.

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70. Fairbrother, R. W.: Immunization of the Horse with the Virus of Poliomyelitis and the Production of an Antiviral Serum, Brit. J. Exper. Path. **11**:43, 1930.

71. This strain is the "pooled mixed virus" of the Rockefeller Institute, adequately described by Fairbrother. This strain has also been used by Rhoads and by Brodie in similar tests, and has been variously designated as the "Fl. M." "P. M. V." and "P. M." strain.

The dose of virus used with these dilutions of serum was only two or three times the minimal infective dose, as the weaker virus of Aycock was used in the experiments. In spite of the contrast in the number of infective doses to the greater number of infective doses used by Fairbrother, the results were consistent. Had the more potent P. M. V. strain been used according to this technic, it is possible that as extensive neutralization would not have been found. Thus, the discrepancy in these results and in the results of workers who have not found the same large amounts of neutralizing substances in the blood of normal adults is probably due to this difference in technic.

Weyer, Park and Banzhaf,[72] using the Aycock strain of virus, found within the limits of their experiments that: "The potency of the virus has apparently no effect upon the amount of a specified serum preparation needed to neutralize it." Since they, like Shaughnessy, Harmon and Gordon, used but 2 to 3 minimal infective doses, their statement can be easily rationalized. They have established still another variation in the technic of the neutralization reaction:

> Total quantities of serum and virus injected were usually 0.3 to 0.4 cubic centimeter and only 0.8 cubic centimeter in two instances. There was always a preponderating ratio of virus to serum varying from 10:1 to 40:1 in some tests. When 1:1 ratios were used, 0.8 cubic centimeter of mixture was injected. Controls were run, and always 0.15 and 0.3 cubic centimeter of virus regularly produced the disease.

Using this method, Weyer, Park and Banzhaf had no difficulty in demonstrating antiviral activity in normal and convalescent human serum and in the blood stream of horses artificially immunized by injections of virus. They determined an additional important point: that serum having neutralizing properties still retained these same properties after absorption with normal monkey brain protein, thus showing that precipitins against monkey brain protein were not identical with the substance responsible for in vitro neutralization. In a recent communication Rhoads [69a] attempted to confirm the observations of Weyer, Park and Banzhaf, but instead of using the virus of Aycock as they did, he performed tests in a similar manner with the potent P. M. V. strain, thus using from 12 to 36 infective doses, although this amount was in a relatively smaller volume than the 2 or 3 minimal infective doses used by Weyer, Park and Banzhaf. It is not surprising, therefore, that with this alteration in the relative amounts of virus and serum, the results should be at variance. In this presentation Rhoads abandoned the technic of utilizing overwhelming quantities of serum with small doses of virus, with which he was successful in demonstrating the exceedingly

72. Weyer, E. R.; Park, W. H., and Banzhaf, E. J.: A Potent Antipoliomyelitic Horse Serum Concentrate and Its Experimental Use in Infected Monkeys, J. Exper. Med. **53**:553, 1931.

small quantities of neutralizing substances in the blood of artificially immunized monkeys, and he deliberately put the serum on the defensive by using larger doses of virus. He brought out two important points: (1) that citrate used to obtain blood plasma by chemical inhibition of the clotting mechanism is directly virucidal, and therefore cannot be used in neutralization tests; (2) that "small differences in incubation period in the inoculated monkeys cannot be regarded as significant," a point on which Harmon, Shaughnessy and Gordon [61] had previously insisted.

Brodie [73] recently published the results of extensive comparative tests of the neutralizing titer of normal and convalescent human serum, which he had the unique experience of executing with an accuracy at least as close as that obtained in the titration of diphtheria toxin and antitoxin. He employed a constant dose of 80 minimal completely paralyzing doses with variable amounts of serum used in successive dilutions of 1 : 2, 1 : 3, 1 : 4 and so on. He also had the unique experience of obtaining mathematically constant preparations of virus from pooled infectious spinal cord preserved in glycerin. This pooled cord was used in an emulsion, but Brodie did not state the exact method of preparation of his emulsion. If these results can be duplicated, an exact quantitative method of titrating serum is available that should supersede all previous methods. As far as can be learned from the data supplied by Brodie, he did not attempt to duplicate the accuracy implied in his protocols. The experience of others has been that a number of discrepancies are encountered in performing this test, so that the mathematical accuracy implied by Brodie is more apparent than real. The methods of Shaughnessy, Harmon and Gordon were criticized by Brodie on the ground that "in many of their neutralization tests, the virus tissue used was not active, since eight of fourteen controls did not contract paralysis with as much as one cubic centimeter of a five per cent emulsion." A careful reading of the report of these authors reveals that they had no controls as such, but always arranged their tests so that one and often more monkeys in a given series of tests became paralyzed, thus providing a self-controlled test of virus potency.

Howitt [74] employed a method similar to that of Shaughnessy, Harmon and Gordon, differing in that, whenever possible, she preferred to eliminate dilution with saline solution. "Different amounts of serum were added in series to 0.3 cc. of either a 2.5 or a 5 per cent virus suspension. Double quantities of serum and virus were mixed, incubated

73. Brodie, M.: A Comparison Between Convalescent Serum and Non-Convalescent Serum in Poliomyelitis, J. Exper. Med. **56**:507, 1932.

74. Howitt, B. F.: Poliomyelitis: I. Production of Antiviral Serums by Inoculation of Goats and Sheep with the Virus of Poliomyelitis, J. Infect. Dis. **50**:26, 1932.

at 37 C. for two hours and then kept on ice overnight. One half of each mixture was injected intracranially into separate monkeys." Howitt noted the same slight irregularities that have been noted by others. Frequently, when a preponderating amount of serum was present in comparison with a smaller amount of virus suspension (1 and 0.3 cc., respectively), failure to neutralize was noted. Such instances are probably further illustrations of "missed infections," originally described by Harmon, Shaughnessy and Gordon,[61] which, occurring in such relations, undoubtedly have an explanation in common with the Neisser-Wechsberg phenomenon.[75] Howitt made a comparison of her method with that of Shaughnessy, Harmon and Gordon and with that of Fairbrother.[70] While she found that the three tests demonstrated the neutralizing property of serum in dilutions, it was clear that only her own method and that of Shaughnessy, Harmon and Gordon were suitable for the most accurate quantitative estimation of neutralizing substance. It was also clear that the dilution of serum that effected neutralization was not of identical magnitude in the two tests, although each gave satisfactory results.

### FACTORS BEARING ON IN VIVO TESTS FOR SERUM ACTIVITY

The incidence of paralysis in relation to the route by which virus is administered has an important bearing on possible in vivo estimations of the efficacy of convalescent and other serums. Until recently these basic data have been nonexistent for a significant number of experimental animals for all except the well known intracerebral method. The general belief as to the relative susceptibility of monkeys in response to the varied routes has been handed down from Flexner and Lewis,[4b] who stated:

> The intracerebral mode of infection is not the only successful one. It has been determined that the virus of epidemic poliomyelitis, when introduced into the body by means of the blood, subcutis, peritoneum, spinal canal and large nerves tends to localize in the spinal cord and brain. Our impression is that infection is readily accomplished by way of the subcutis and less readily by the peritoneal cavity.

Only the routes that have a bearing on the experimental testing of serum will be considered. Methods other than introduction directly into nerve tissue are generally believed to be more uncertain in producing experimental infection. Amoss [76] stated that the intraperitoneal method is uncertain and that it is one by which only large doses of virus are occasionally effective. He also considered the subcutaneous and intravenous methods of giving the virus as producing infection only rarely.

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75. Neisser, M., and Wechsberg, F.: Ueber die Wirkungsart bactericider Sera, München. med. Wchnschr. **48**:697, 1901.

76. Amoss, H. L.: Communicability and Serum Treatment of Poliomyelitis, New York State J. Med. **22**:256, 1922.

The special significance of the latter fact will be brought out when the "therapeutic test" of serum proposed by Flexner and Amoss is reviewed (p. 1204).

The intracutaneous method of injecting virus is known to result occasionally in typical paralysis; this fact has been observed by many [57] who have attempted to effect artificial immunization by the method. The numerical incidence of positive results is unknown. Brodie [77] had the unique experience of obtaining regular infection by this route. It may be that the advanced potency of the strain of virus which he used has a bearing on his results, as he has been able to inject from 15,000 to 20,000 infective doses, as measured by the intracerebral method, into a single skin bleb.

Intranasal inoculation followed by typical paralysis has been reported by many authors,[78] but the observations of all who have had an extensive experience with the method have been that there are many failures. For example, Fairbrother and Hurst,[79] using the same strain of virus as Flexner and Rhoads, obtained only three successful infections of 12 animals thus inoculated. They stated that "infection resulted very inconstantly." Howitt [80] determined that only 53 per cent of monkeys were susceptible to intranasal instillation, while Harmon, Shaughnessy and Gordon [29] obtained only 27 (56.2 per cent) successful infections among 48 monkeys by repeated intranasal instillation of virus, even when the infection was promoted in certain animals by extranasal factors. Rhoads [81] has apparently been more successful in producing infection by the nasal route, as the "instillation of one cubic centimeter of a five per cent virus suspension into each nostril, repeated daily for three days,

77. Brodie, M., quoted by Harrington.[38]

78. (*a*) Flexner, S., and Lewis, P. A.: Experimental Epidemic Poliomyelitis in Monkeys, J. A. M. A. **54**:1140 (April 2) 1910. (*b*) Levaditi, C., and Landsteiner, K.: Etude expérimentale de la poliomyélite aiguë (sixième note), Compt. rend. Soc. de biol. **68**:417, 1910. (*c*) Flexner, S., and Clark, P. F.: A Note on the Mode of Infection in Epidemic Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **10**:1, 1912. (*d*) Levaditi, C., and Danulesco, V.: La pénétrabilité du virus de la poliomyélite à travers la muqueuse nasal et l'action préventive des antiseptiques appliqués localement, Compt. rend. Soc. de biol. **73**:252, 1912. (*e*) Flexner, S., and Amoss, H. L.: Experiments on the Nasal Route of Infection in Poliomyelitis, J. Exper. Med. **31**:123, 1920. (*f*) Demme, H.: Ueber experimentelle Poliomyelitis, Deutsche Ztschr. f. Nervenh. **116**:156, 1930. (*g*) Flexner, S.: Simultaneity in the Onset of Poliomyelitis, Science **74**:601, 1931.

79. Fairbrother, R. W., and Hurst, E. W.: The Pathogenesis and Propagation of the Virus in Experimental Poliomyelitis, J. Path. & Bact. **33**:17, 1930.

80. Howitt, B. F.: Poliomyelitis: II. Comparison of Intramuscular Injection with Combined Intraspinal and Intravenous Injection of Convalescent Serum in the Treatment for Experimental Poliomyelitis in Monkeys, J. Infect. Dis. **50**:47, 1932.

81. Footnote 69.

was practically uniformly successful in causing infection in normal animals." Flexner [73c] stated: "No other means (than nasal instillation) of producing the infection in monkeys gives a corresponding regular result." The previous report of Flexner and Amoss from the same laboratory had emphasized that: "Certain monkeys are highly refractory to inoculation via the nares with the virus of poliomyelitis." The consensus seems to deny that monkeys are universally susceptible to infection by way of the nares. The results of Howitt and of Harmon, Shaughnessy and Gordon are in as good agreement as to the number of animals that are susceptible (53 and 56 per cent, respectively) as such small series permit. The objection of a difference in infectious potency of the virus preparations cannot be raised since Harmon, Shaughnessy and Gordon used the same virus as that used by Rhoads and by Flexner, the highly potent M. V. strain. Using the special technic of a preliminary lavage of the nasal passage with an acid buffer solution, Schultz and Gebhardt and Faber and Gebhardt [82] have recently been successful in obtaining about 95 per cent of infections with three instillations of virus on a single day. Unless such a special technic proves to be uniformly successful in the hands of other investigators, determinations of the effect of serum in modifying infection induced by the nasal route are not practicable unless a large number of animals are used and the results are considered statistically. This has been the method adopted by Howitt [83] in demonstrating the in vivo activity of antiviral animal serums.

Intraspinal [84] and intracisternal [85] inoculations are consistently successful with an adequate amount of virus which need not be many times more than the infectious dose as estimated by intracerebral injection. It is doubtful whether either of these methods produces a less severe infection than the intracerebral method, but they have the positive advantage of avoiding trauma to the nervous parenchyma. The introduction of

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82. Schultz, E. W., and Gebhardt, L. P.: Observations on the Intranasal Route of Infection in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **30**:1010, 1933. Faber, H. K., and Gebhardt, L. P.: Localizations of Poliomyelitic Virus During Incubation Period After Intranasal Instillation in Monkeys, ibid. **30**:879, 1933.

83. Footnotes 74 and 80.

84. Flexner, S., and Lewis, P. A.: Epidemic Poliomyelitis in Monkeys: A Mode of Spontaneous Infection, J. A. M. A. **54**:535 (Feb. 12) 1910. Neustaedter, M., and Thro, W. C.: Experimental Poliomyelitis Produced in Monkeys from the Dust of the Sick Room, New York M. J. **94**:813, 1911. Footnote 21b.

85. Flexner, S., and Rhoads, C. P.: A Method for the Determination of the Activity of Antipoliomyelitis Serum, Proc. Nat. Acad. Sc. **15**:609, 1929. Hurst, E. W.: Further Observations on the Pathogenesis of Experimental Poliomyelitis: Intrathecal Inoculation of the Virus, J. Path. & Bact. **35**:41, 1932. Rhoads.[57b]

the virus directly into the nervous system, either by the direct intracerebral method or by inoculation into a peripheral nerve,[86] is known to result invariably in the typical fulminating infection in experimental animals which is little affected by the administration of serum, even if the serum is given coincidentally with the virus but by another route.

### PASSIVE SERUM PROTECTION AND SERUM TREATMENT OF THE EXPERIMENTAL DISEASE

Notwithstanding the early success reported in passive protection of monkeys with "immune serum" (p. 1189), recent attempts to modify the course of the experimental disease as established by intracranial inoculation of the virus have met with little success. The report of Rosenow [30] is an exception, since in his communication evidence was presented that this author's antistreptococcus horse serum had been effective in lowering the incidence of paralysis and the fatality rate in animals in which the disease had been established by intracerebral inoculation of virus a few days prior to treatment by serum. The recent reports of the use of convalescent serum in similar attempts have been in marked contrast to the outcome just cited.

Howitt [80] stated that there was "encouraging evidence of the in vivo protective properties of the antipoliomyelitic sheep serum" injected before intracranial inoculation of the virus. Complete protection was obtained when doses of 20 cc. were administered intravenously in 3 or 4 cases and also in one half of the animals which received doses of 80 cc. intramuscularly; doses of 20 cc. gave partial protection in some monkeys but not in others. The same author [74] attempted to make an experimental comparison of the effects of intramuscular administration of serum and of the combined intraspinal-intravenous route in 41 monkeys infected by the intracerebral route. She stated: "The combined intraspinal and intravenous method, as used in this experiment, was not so effective as the intramuscular method as judged by the high mortality in the animals treated with the combined method, as compared with those treated by the intramuscular method." A scrutiny of her protocols reveals the startling fact that the intraspinal-intravenous administration of serum to these monkeys resulted in a poorer outcome in the treated

86. Flexner, S., and Lewis, P. A.: The Transmission of Epidemic Poliomyelitis to Monkeys: A Further Note, J. A. M. A. **53**:1913 (Dec. 4) 1909. Leiner, C., and von Wiesner, R.: Experimentelle Untersuchungen über Poliomyelitis acuta anterior, Wien. klin. Wchnschr. **23**:91, 1910. Marinesco, G.: De la transmission du virus de la poliomyélite par le nerf périphérique et ses rapports avec les infections ascendantes, Compt. rend. Soc. de biol. **70**:286, 1911. Flexner, S.; Clark, P. F., and Amoss, H. L.: A Contribution to the Pathology of Epidemic Poliomyelitis, J. Exper. Med. **19**:205, 1914. Hurst, E. W.: A Further Contribution to the Pathogenesis of Experimental Poliomyelitis: Inoculation into the Sciatic Nerve, J. Path. & Bact. **33**:1133, 1930. Fairbrother and Hurst.[79]

animals than in the untreated controls. There was a consistent incidence of paralysis and death in the monkeys, regardless of whether the serum was given before the intracranial infecting dose of virus, at the same time, immediately after or even in the preparalytic or early paralytic stage of the disease. There was evidence of protection in about half of the animals when the serum was given intramuscularly twenty-four hours before or after the intracranial infecting dose of virus. Even the latter animals demonstrate an outcome but little better than that showed by the untreated controls, so that the alleged protective effect of serum known to be highly active in in vitro tests was not strikingly displayed by this method.

Harmon, Shaughnessy and Gordon [29] have had similar experiences in attempting to demonstrate an in vivo protective action of human and monkey convalescent serum. Independently, they have executed experiments similar to those of Howitt, except that they employ both convalescent human and monkey serum in attempting to modify the experimental disease produced in monkeys by intracerebral inoculation of virus. When they allowed the disease to progress even to the relatively early preparalytic stage—in many instances this stage was diagnosed in animals as long as from forty-eight to seventy-two hours prior to paralysis by means of recording of the temperature and examinations of the spinal fluid [87]—they were unable to determine whether serum administered by any route or by a combination of routes had any effect on the appearance, extent or outcome of the paralysis. Indeed, when human convalescent serum was given to monkeys, especially by the intraspinal route, it appeared that the aseptic meningitis set up in this way hastened the advent of paralysis. Thus the experience of Park [88] of a deleterious effect of the intraspinal injection of antiviral horse serum in human preparalytic poliomyelitis has an experimental counterpart. Even when treatment was begun within twenty-four hours of the intracerebral inoculation of virus, they were unable to observe other than the usual outcome in 20 animals. Weyer, Park and Banzhaf,[72] Rhoads,[69a] Fairbrother [70] and Schultz and Gebhardt [89] have reported similar experiences.

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87. Harmon, P. H.; Shaughnessy, H. J., and Gordon, F. B.: Preparalytic Poliomyelitis in the Monkey. Changes in Temperature, Spinal Fluid and Erythrocyte Sedimentation, J. Prev. Med. **5**:115, 1931. Kramer, S. D.; Hendrie, K. H., and Aycock, W. L.: Rise in Temperature Preceding the Appearance of Symptoms in Experimental Poliomyelitis, J. Exper. Med. **51**:933, 1930.

88. Park, W. H.; Weyer, E. R., and Banzhaf, E. J., quoted by Neal, J. B., in International Committee for the Study of Infantile Paralysis: Poliomyelitis, Baltimore, Williams & Wilkins Company, 1932, p. 236.

89. Schultz, E. W., and Gebhardt, L. P.: On the Prophylactic and Therapeutic Value of Specific Immune Serum in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **31**:260, 1933.

By employing the method of exsanguination transfusion in which a large amount (180 cc.) of whole homologous blood from convalescent monkeys was transferred to each of 2 other monkeys from several animal donors, an absolute resistance to a large intracerebral test dose of virus was demonstrated,[29] while the disease promptly developed in a control animal. Thus, apparently only such heroic methods suffice to demonstrate regularly a resistance to the drastic intracerebral introduction of the virus. The number of animals required to demonstrate passive resistance precludes the use of any of these methods as a practical in vivo demonstration of virucidal properties of serums. Fairbrother [70] and Fairbrother and Morgan [90] similarly decided "that the passive protection test is entirely unreliable."

Owing to the unsatisfactory experiences just enumerated, other less drastic methods of induction of the experimental disease through inoculation with virus have been tried. In the hands of many authors the intranasal introduction of virus has resulted in the active disease in only from 53 to 56 per cent of susceptible monkeys. Those who have been successful in producing the disease regularly in this way have considered that utilization of this method offered an ideal test for demonstrating the preventive and curative properties of serum. Rhoads [91] has been able to block infection regularly with virus administered into the nares, followed by the intraspinal injection of a convalescent serum. When the same method was applied to the in vivo assay of antiviral horse globulin, irregularities were noted. That the method is not a reliable one is indicated in Rhoads' own protocols in which antidiphtheritic globulin protected as well as did the antiviral horse globulin. Although he termed this experiment a "therapeutic test" the conditions are those of attempted passive protection during the period of incubation following intranasal administration of the virus. Weyer, Park and Banzhaf [72] performed experiments similar to those of Rhoads. Their results are at variance with those of Rhoads in that in most instances convalescent serum administered intraspinally failed to protect the animal while in 8 of 9 instances antiviral horse globulin gave protection when given intraspinally. When the globulin was given intravenously the protection was much less constant. Weyer and his co-workers outlined other protective experiments in which the intranasal test dose of virus was given from one to four weeks after a protective dose of serum had been administered parenterally. The concentrated horse globulin was more consistent in its protective effects than human convalescent serum.

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90. Fairbrother, R. W., and Morgan, W. T. J.: Further Observations on the Immunization of the Horse with the Poliomyelitis Virus, Brit. J. Exper. Path. **11**:298, 1930.

91. Rhoads, C. P.: Unpublished experiments. Footnote 69a.

The results obtained by Howitt [80] and by Harmon, Shaughnessy and Gordon [29] are at variance with these experiments, although an identical technic was used. In these experiments the effect of serum was debatable, since in many of the experiments of Howitt not a single animal, including unprotected controls, contracted the disease. The results of Harmon, Shaughnessy and Gordon were similar to their previous determinations of the effectiveness of the nasal portal of infection. No difference in the incidence of the disease was noted in the group of animals protected with convalescent monkey serum and in those given normal monkey serum.

Another variation in this type of experimentation is that utilized by Brodie [77] who has been able regularly to effect passive protection with as little as 6 cc. of convalescent serum when the test dose of virus was given intracutaneously. If these experiments can be repeated this will be an ideally convenient method of testing serum for protective activity. Unfortunately, the experience of other investigators [57] with the intracutaneous route of virus administration is not in accord with that of Brodie, so that the method cannot be accepted without adequate confirmation.

### THE SO-CALLED "THERAPEUTIC TEST" OF FLEXNER AND AMOSS

While engaged in early work on the properties of the virus of poliomyelitis, Flexner and Amoss [92] noted that only occasional overwhelming doses of virus given intravenously sufficed to produce the experimental disease. Even if mild degrees of irritation of the meninges or choroid plexus were produced, infection occurred regularly. They proposed to test serum in this way, since the only substance that prevented infection under these conditions was serum containing neutralizing substances. However, on reinvestigation [93] of this phenomenon, they found that such a remarkable delicacy of adjustment existed between the blood stream and the meningeal choroid plexus barrier that substances which were but faintly irritating, such as compatible homologous serum, physiologic solution of sodium chloride and Ringer's and Locke's solutions, upset this barrier sufficiently to allow the virus contained in the blood to produce an infection within the central nervous system. Indeed so extraordinarily delicate was this mechanism found to be that a puncture of the lumbar subarachnoid space followed by readministration of the same fluid occasionally resulted in an infection. If a slight hemorrhage supervened during such a puncture the possibility of infection became a

92. Flexner, S., and Amoss, H. L.: Localization of the Virus and Pathogenesis of Epidemic Poliomyelitis, J. Exper. Med. **20**:249, 1914.

93. Flexner, S., and Amoss, H. L.: The Relation of the Meninges and Choroid Plexus to Poliomyelitic Infection, J. Exper. **25**:525, 1917.

certainty. It was further emphasized by Flexner and Amoss that a rigid technic must be used in the preparation of virus emulsions, and that freshly prepared emulsions rather than glycerinated virus should be used for such experiments. Thus, it appears that such a test is too delicate and exacting to be of value as a practical in vivo test of serum.

On theoretical grounds it should be pointed out that rather than a "therapeutic test," the conditions of such experiments are those of passive protection in the early days of the incubation period. Largely on the basis of this test, Amoss and Eberson [94] claimed that the serums of Rosenow and of Nuzum were without therapeutic value. Nuzum pointed out the shortcomings of the proposed therapeutic test of Flexner and Amoss when he used the same test to reexamine his antistreptococcus serum with results diametrically opposite to those of Amoss and Eberson. In addition to criticizing the test on theoretical grounds, Nuzum [95] noted many irregularities in the method: "It appears that even specific immune monkey serum which is known to possess neutralizing properties for virus may not suffice to prevent infection under the conditions of this test."

Recent workers have had experiences akin to those of Nuzum. Harmon, Shaughnessy and Gordon [29] performed an extensive number of experiments using both human and monkey convalescent serum, and were unable to correlate the in vitro neutralizing power of the serum with the results obtained by Flexner and Amoss. The basic fact that the introduction of many times the intracerebral paralyzing dose into the vascular system seldom leads to paralysis has been found to be true, but the use of freshly prepared virus suspensions has not been found necessary as glycerinated virus emulsions prepared by washing the cord fragments were entirely innocuous. Howitt [74] likewise noted irregularities in the practical application of this method. The method does not appear to furnish a practicable in vivo test of the therapeutic activity of serum.

### ANTISTREPTOCOCCUS SERUMS (ROSENOW AND NUZUM AND WILLY)

As pointed out later (p. 1245), the practical results obtained in the treatment of both preparalytic and early paralytic poliomyelitis with the antistreptococcus serums have been equal to those obtained with human convalescent serum. Since there is no method for directly testing the therapeutic activity of antipoliomyelitic serums in the laboratory,

94. Amoss, H. L., and Eberson, F.: Therapeutic Experiments with Rosenow's Antipoliomyelitic Serum, J. Exper. Med. **27**:309, 1918; An Experimental Test of Nuzum's Antipoliomyelitic Horse Serum, J. Exper. Med. **28**:323, 1918.

95. Nuzum, J. W.: The Production of an Antipoliomyelitic Serum, J. A. M. A. **68**:24 (Jan. 6) 1917.

the practical results obtained with serum constitute an important point in favor of the serum. Recent work (pp. 1182 to 1186) tends to minimize or altogether contradict the importance of streptococci in the pathogenesis of the lesions of poliomyelitis, so that these serums are not favored on theoretical grounds.

Rosenow [96] was the first to produce an antistreptococcus serum in the horse. The methods that were used can be found in his publications.[97] Working independently, Nuzum [95] and Nuzum and Willy [98] produced a similar serum. These authors furnished abundant direct evidence that these serums neutralized the virus of poliomyelitis in adequately controlled in vitro neutralization tests. Using the so-called "therapeutic test" of serum devised by Flexner and Amoss, Amoss and Eberson [94] stated that the serums of Rosenow and of Nuzum and Willy were devoid of protective power. Nuzum,[99] however, directly refuted the experiments of Amoss and Eberson and at the same time pointed out the shortcomings of the Flexner-Amoss test. In addition, Nuzum [66] again demonstrated that his serum contained neutralizing substances. A like position has since been maintained by Rosenow,[30] who has furnished statistical evidence of the experimental activity of his serum in the treatment and prophylaxis of the experimental disease in monkeys. Such a positive result is unique, as the general experiences with treatment and prophylaxis of the experimental disease have been disappointing.

Recently, Stewart and Hazelbauer [68] carried out in vitro neutralization tests with both concentrated and unconcentrated samples of Rosenow's serum. Under the conditions of their experiments this serum was found devoid of neutralizing power. Morgan and Fairbrother [100] likewise failed to detect neutralizing substances in a commercial sample of Rosenow's serum. Even in the most recent report by Rosenow [30] himself, affirmation of the previous observations of the presence of neutralizing substances against the virus appears. It is noteworthy that Rosenow recorded discrepancies between his observations and the gen-

96. Footnotes 1d and 67.

97. (*a*) Rosenow, E. C., and Nickel, A. C.: Treatment of Acute Poliomyelitis with Poliomyelitis Antistreptococcus Serum: Results from 1921 to 1925, Am. J. Dis. Child. **33**:27 (Jan.) 1927. (*b*) Footnote 30.

98. Nuzum, J. W., and Willy, R. G.: Specific Serum Therapy of Epidemic Poliomyelitis, J. A. M. A. **69**:1247 (Oct. 13) 1917.

99. Nuzum, J. W.: The Protective Properties of Antipoliomyelitic Horse Serum, J. Infect. Dis. **23**:309, 1918.

100. Morgan, W. T. J., and Fairbrother, R. W.: The Concentration of the Protective Substance in Antipoliomyelitis Serum, Brit. J. Exper. Path. **11**:512, 1930.

eral experience of many authors (p. 1223) who have found a widespread occurrence of neutralizing substances in the blood of "normal" persons. For example, he found that normal human and monkey serum contained neutralizing substances against the virus in only 16 per cent of 7 instances. These discrepancies can scarcely be attributed to technical variations or differences in the strain of virus.

### ANTIVIRAL ANIMAL SERUMS

Until recent years the production of an antiviral serum in nonsusceptible species had been received with skepticism largely as the result of the early failures of Flexner [101] and of Flexner and Lewis [45c] to produce an active serum in a horse after many months of repeated injections of virus. The report of Neustaedter and Banzhaf,[102] who claimed to have produced a neutralizing serum in a horse, had been ignored on technical grounds. Attempts of Leake [103] and of Dixon and Rucker [104] to confirm the latter report were unsuccessful. Both Flexner [101] and Tsen [105] were unable to obtain a serum from rabbits that would neutralize the virus. Pettit [106] produced a neutralizing serum in a sheep as a result of the intravenous injection of emulsions of virus, but since it had been shown by Flexner and Lewis [107] and by Stewart and Hazelbauer [68] that normal sheep serum occasionally neutralized the virus, acceptance of the theoretical possibility of producing an antiviral animal serum was further withheld. Indeed, in the later reports from the Pasteur Institute [108] describing the preparation of antiviral horse serum more reliance was placed on the clinical efficiency of the serum than on a few neutralization tests. Within recent years, there have appeared

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101. Flexner, S.: The Contributions of Experimental to Human Poliomyelitis, J. A. M. A. **55**:1105 (Sept. 24) 1910.

102. Neustaedter, M., and Banzhaf, E. J.: An Antipoliomyelitic Horse Serum, J. A. M. A. **68**:1531 (May 26) 1917.

103. Leake, J. P.: Experimental Poliomyelitis, U. S. Pub. Health Service, Hyg. Lab. Bull. no. 111, 1918, p. 21.

104. Dixon, S. G., and Rucker, J. B., Jr.: Failure to Obtain Potent Serum from Horse Injected with Poliomyelitic Material, J. Infect. Dis. **23**:543, 1918.

105. Tsen, E. T. H.: Experiments on the Production of Antipoliomyelitic Serum in Rabbits, J. Immunol. **3**:213, 1918.

106. Pettit, A.: Sur la préparation d'un sérum neutralisant le virus de la poliomyélite, Compt. rend. Soc. de biol. **81**:1087, 1918.

107. Flexner, S., and Lewis, P. A.: Experimental Poliomyelitis in Monkeys: Eighth Note: Further Contributions to the Subjects of Immunization and Serum Therapy, J. A. M. A. **55**:662 (Aug. 20) 1910.

108. (*a*) Pettit, A.: Sérum antipoliomyélitique, Bull. gén. de thérap. **176**:389, 1925; La poliomyélite antérieure aiguë: Biologie, Gaz. d. hôp. **104**:221, 1931. (*b*) Stefanopoulo, G. J.: Sérothérapie antipoliomyélitique, Thèse de Paris, 1924.

many reports [109] from widely scattered and independent workers proving conclusively that neutralizing substances can be produced by the inoculation of horses and other nonsusceptible species. Weyer, Park and Banzhaf,[72] Fairbrother and Morgan [110] and Howitt [74] clarified the controversial points, finding that the requisite factors for the production of such a serum are a long period of weekly inoculations lasting at least six or eight months and a route of administration other than the intravenous one. The failures of certain other authors are rationalized by these factors and by the finding that certain individual animals did not respond to immunization even after a protracted period. Howitt [111] found goats and sheep to be satisfactory animals for immunization.

Attempts have been made to produce a therapeutic serum in monkeys by active immunization. Pettit [58a] selected the species Cynocephalus hamadryas, a common species of larger monkey, and carried out a successful course of immunization by the subcutaneous and intraperitoneal routes. Pettit and his co-workers [112] similarly immunized a chimpanzee. In both instances a potent neutralizing serum was obtained in much less time than was required for immunization of nonsusceptible animals. Pettit favored the chimpanzee both on account of its size and because the blood of the anthropoids can be typed and cross matched perfectly with the blood groups of man.[113] Flexner and Lewis [45c] believed that the neutralizing content of convalescent serum could be increased by artificial active immunization with virus. Although they employed the method empirically to "reenforce" the serum of convalescent monkeys,

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109. (*a*) Jonesco-Mihaesti, C.; Tupa, A.; Wisner, B., and Mesrobeanu, I.: Etudes sur la poliomyélite en Roumanie, Arch. roumaines de path. expér. et de microbiol. **2**:217, 1929. (*b*) Howitt, B. F.; Shaw, E. B.; Thelander, H., and Limper, M.: The Immunization of Goats and Sheep to Poliomyelitis Virus, J. A. M. A. **96**:1280 (April 18) 1931. (*c*) Footnote 74. (*d*) Neustaedter, M.: Antipoliomyelitis Horse Serum: Preparation and Use, J. A. M. A. **96**:933 (March 21) 1931. (*e*) Schultz, E. W., and Gebhardt, L. P.: Antipoliomyelitis Serum Production in the Horse, Proc. Soc. Exper. Biol. & Med. **28**:412, 1931; Immune Serum Production in Poliomyelitis Refractory Animals, J. Immunol. **26**:93, 1934. (*f*) Weyer, E. R.; Park, W. H., and Banzhaf, E. J.: Refined Antipoliomyelitis, Am. J. Path. **5**:517, 1929.

110. (*a*) Fairbrother, R. W., and Morgan, W. T. J.: Observations on the Production of Antipoliomyelitis Serum in Horses and Distribution of Antibody Among Serum Fractions, Lancet **2**:584, 1931; (*b*) footnotes 70 and 90.

111. Howitt, B. F.: (*a*) Poliomyelitis: IV. Further Studies on the Immunization of Sheep to the Virus of Poliomyelitis, with a Comparison of Neutralization Tests, Using the Old and a Recent Strain of Virus, J. Infect. Dis. **53**:145, 1933; (*b*) footnote 74.

112. Pettit, A.; Erber, B., and Kolochine, C.: Utilisation du chimpanzé pour la préparation du sérum antipoliomyélite, Compt. rend. Soc. de biol. **109**:821, 1932.

113. Landsteiner, K., and Miller, C. P.: Serological Studies on the Blood of the Primates, J. Exper. Med. **42**:841, 853 and 863, 1925.

they did not establish this assumption by actual tests of serum. Rhoads [114] recently showed the truth of the assumption by demonstrating an additional acquisition of neutralizing substance after active immunization of convalescent monkeys.

Laboratory tests of the various types of antiviral animal serums indicate that the activity of these serums differs in no important respect from that of human convalescent serum. While no actual comparative tests were reported by Howitt [74] or by Neustaedter and Banzhaf,[102] the titers of neutralizing substance reached after many months of immunization were of high order. Fairbrother,[70] Weyer, Park and Banzhaf [72] and Schultz and Gebhardt [109e] carried out comparative neutralization tests between their serums and human convalescent serum. Fairbrother and Weyer, Park and Banzhaf obtained serum identical in potency with human convalescent serum, while Schultz and Gebhardt obtained a serum more potent than the average human convalescent serum.

It is certain that the neutralizing principle contained in these antiviral animal serums is identical with that present in the convalescent serum of man and of monkeys, since Weyer, Park and Banzhaf [72] determined the important fact that absorption of protein precipitins of the spinal cord of monkeys from the antiviral serums leaves the neutralizing principle in the absorbed serum. However, these experiments were not performed quantitatively, so that it is possible that anticord precipitins play an adjuvant rôle in ordinary neutralization tests with antiviral serums. The practical results that have been obtained in treating poliomyelitis in man and in treating experimentally induced poliomyelitis have been presented in another place (pp. 1201 and 1245-1246).

### FACTORS BEARING ON NEUTRALIZING TITER OF SERUMS; STORAGE OF SERUM; CONCENTRATION AND PURIFICATION OF ANTIPOLIOMYELITIC SERUMS

Both convalescent and normal human serums vary greatly in their ability to neutralize the virus. Indeed, it has been shown that certain specimens of human convalescent serum are devoid of neutralizing properties. Factors bearing on variations in concentration of the neutralizing substance have been largely ignored until recent years. The optimum time for collecting serum for therapeutic purposes following a paralytic attack of poliomyelitis has not been definitely determined. Evidence is available indicating that there is a greater probability of obtaining a more potent serum months after an attack than a few days after paralysis

114. Rhoads, C. P.: Reinforcement of Convalescent Antipoliomyelitic Serum in the Monkey, J. Exper. Med. **53**:137, 1931.

ensues. Aycock and Kramer [115] noted that the serum of a paralytic monkey failed to neutralize the virus when tested three and six weeks after paralysis occurred, but when it was tested six months after the disease, neutralization was obtained. Park [116] is said to have tested the serum in a number of cases in the New York epidemic of 1931 and to have found that "the antibody first appeared some weeks after convalescence." The results of Burnet and Macnamara [117] and of Shaughnessy, Harmon and Gordon [53] indicate that the serum from subjects with paralysis of longer standing was more effective in neutralization tests than that taken within a year after the onset of paralysis. Recent work (p. 1192) indicating that both normal and convalescent persons of blood group B (Moss III) have a greater concentration of neutralizing substance in their serum appears to demonstrate the desirability of employing these persons as donors of serum when possible. These results are based on sparse data, and until more comprehensive investigations can be carried out, the foregoing conclusions must be viewed as tentative.

Howitt [118] recently made comparative tests of human serums from convalescents with and without serum treatment. She found that the serum of 63.6 per cent of 22 patients failed to neutralize the virus while the serum of only 55 per cent of 20 untreated patients failed to neutralize it. The rather high percentage of serums failing to inactivate the virus in these tests might, in part, be explained by the fact that many of the patients were recent convalescents. Howitt also stated: "Patients showing complete recovery after transient or only slight paralysis give more evidence of the production of a potent serum than those in whom severe paralysis develops." All these findings emphasize the need of testing the in vitro neutralizing power of serum prior to its being utilized in treatment.

Recently, qualitative immunologic differences have been found between passage strains of virus and virus freshly isolated from man. As this phenomenon was first described by Australian investigators,[119]

115. Aycock, W. L., and Kramer, S. D.: Immunity to Poliomyelitis in a Southern Population as Shown by the Neutralization Test, J. Prev. Med. **4**:201, 1930; Immunity to Poliomyelitis in Mothers and the Newborn as Shown by the Neutralization Test, J. Exper. Med. **52**:437, 1930. Footnote 58b.

116. Park, W. H., quoted by Harrington, H., in International Committee for the Study of Infantile Paralysis,[11] p. 148.

117. Burnet, F. M., and Macnamara, J.: The Activity of Stored Antipoliomyelitic Serum in Experimental Poliomyelitis, M. J. Australia **2**:851, 1929.

118. Howitt, B. F.: Poliomyelitis: III. Results of in Vitro Neutralization Tests on Serums of Both Treated and Untreated Poliomyelitic Patients, J. Infect. Dis. **51**:574, 1932.

119. Burnet, F. M., and Macnamara, J.: Immunological Differences Between Strains of Poliomyelitic Virus, Brit. J. Exper. Path. **12**:57, 1931.

it was assumed that there was a different strain of poliomyelitis virus responsible for the disease in the antipodes, until Weyer [120] and Flexner [55] pointed out that a strain of the virus isolated from the New York epidemic of 1931 behaved variably in cross-neutralization tests with convalescent serum and with antiviral animal serum. Paul and Trask [121] and Howitt [111a] have investigated in detail these differences in strains of virus in relation to the antiviral content of serum from recent convalescents. The latter authors found that serum from patients of the recent epidemics neutralized the corresponding virus in nearly every instance while the same serums frequently failed to show antiviral properties against a monkey passage virus. Such results have a profound practical implication in that it seems best to test therapeutic serums against

*Comparison of Incidence of Neutralizing Serums from Persons Convalescing from Poliomyelitis with Serums from Normal Persons*

| Author | Source of the Serum | Convalescent Human Serum | | | Normal Human Serum | | |
|---|---|---|---|---|---|---|---|
| | | Number | Positive | Per Cent | Number | Positive | Per Cent |
| Aycock and Kramer [58b, 115] | Boston and Atlanta | 17 | 15 | 88.2 | 96 | 57 | 59.4 |
| Kramer and Aycock (Proc. Soc. Exper. Biol. & Med. **29**: 98, 1931) | Boston and Bedford, Mass. | .. | .. | .... | 88* | 39 | 44.3 |
| Shaughnessy, Harmon and Gordon [53] | Chicago | 14 | 8 | 57.1 | 24 | 16 | 66.6 |
| Schultz and Gebhardt (Proc. Soc. Exper. Biol. & Med. **28**: 409, 1931) | San Francisco | 4 | 2 | 50.0 | 32 | 18 | 56.2 |
| Jungeblut [61] | New York | 26 | 15 | 57.6 | 30 | 17 | 56.7 |

* The serum was obtained from children aged from 5 to 15 years.

the current virus rather than against laboratory passage strains. This statement is made notwithstanding the well known difficulty in implanting into monkeys epidemic virus from man. Paul and Trask [121] have shown that monkeys are reliable test animals for the new virus after passage through a few generations.

There is as yet no unanimity of opinion pointing to the possible superiority of convalescent serum over neutralizing "normal" human serum to be derived from the results of comparisons of the neutralizing power of these serums. There are available at the present time but four reports that deal in significant numbers with serums of both classes. These are presented in the table. It can be seen that Aycock and Kramer

120. Weyer, E. R.: Immunological Differences Between a Strain of Monkey Virus and Human Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **29**:289, 1931.

121. (*a*) Paul, J. R., and Trask, J. D.: Footnote 27c; (*b*) Trask, J. D., and Paul, J. R.: Neutralizing Antibodies in Abortive Poliomyelitis, J. Exper. Med. **58**:531, 1933.

have produced results that favor human convalescent serum as having a greater concentration of neutralizing substance than normal human serum, while the results of Shaughnessy, Harmon and Gordon and of Schultz and Gebhardt favor normal human serum. As the last two groups of authors dealt with a smaller number of serums, it is possible that chance selection played a more important rôle in their results than in those of Aycock and Kramer. According to the results of Jungeblut, there is little choice between convalescent and normal human serum. More extensive data are needed to furnish a satisfactory answer to this question.

Only three brief reports can be found on the potency of serum as affected by storage. Burnet and Macnamara [117] tested oxalated convalescent plasma stored in sealed ampules without preservatives after three years and found that the plasma still contained neutralizing substances. Brodie [122] stated that he had found a two year old sample of pooled convalescent serum that contained neutralizing substances. Howitt [111a] found the titer of human convalescent serum undiminished after storage for one year. There were no comparative estimations of antibody titer made prior to storage in these investigations with the exception of the last mentioned report so that the possibility of some deterioration in antibody content during storage cannot be totally denied.

Filtration through bacteria-tight filters of the Berkefeld or Seitz type was said by Rhoads [69a] to remove the neutralizing antibody from globulin concentrates of antiviral horse serum. However, it is to be noted that filtration through a Berkefeld filter constituted one of the steps in the preparation of a sterile globulin concentrate as described by Weyer, Park and Banzhaf.[72] Morgan and Fairbrother [95] likewise employed Seitz filtration without seriously impairing the potency of protein fractions. Added evidence that Berkefeld filtration does not remove significant quantities of the neutralizing substance is given by Rhoads,[69a] who stated that convalescent human and monkey serum could be treated in this way without loss of the neutralizing substance.

Most work on the concentration of serums and on the purification of the neutralizing substance has been done on the antiviral horse serums produced in recent years. Much earlier, Rosenow [97a] employed a concentrated globulin preparation of his antistreptococcus horse serum. No data are furnished as to the method of preparation of the Rosenow concentrate. Weyer, Park and Banzhaf [72] and Morgan and Fairbrother [123] have elaborated an effective method of concentrating the neutralizing principle from antiviral horse serums. These two groups

122. Brodie, M., quoted by Harrington, H., in International Committee for the Study of Infantile Paralysis,[11] p. 147.

123. Footnotes 100 and 110a.

of investigators are not in agreement on the fraction containing the greatest amount of the neutralizing substance. The former authors stated that the pseudoglobulin fraction contains most of the active principle, while the results of the latter group demonstrate that the euglobulin fraction contains the greater amount. Weyer, Park and Banzhaf have adopted the well known method of Banzhaf [124] for the purification of diphtheria antitoxin by separation of the pseudoglobulin fraction of immune horse serum. By this method, they have succeeded in obtaining globulin preparations averaging three or four times the potency of both the original serum and the average pooled human convalescent serum. The method results in a 50 per cent loss in the total amount of antibody but effects a volume concentration of about 80 per cent. So far as can be learned from the data given, these authors did not estimate the amount of neutralizing substance contained in the other serum fractions. In view of the results of Morgan and Fairbrother it is highly probable that a part of the lost antibody was contained in the other serum fractions. These authors separated the serum proteins systematically by several methods and found that a certain quantity of the neutralizing principle was carried in the pseudoglobulin and albumin fractions as well as in the euglobulin fraction. They demonstrated that from ten to fifty times as small a quantity of euglobulin (0.13 to 0.5 mg. in some experiments) neutralized the virus as pseudoglobulin from the same serum. Evidence was offered that as immunization proceeds a relative shift in concentration between the euglobulin and pseudoglobulin fractions occurs.

That the neutralizing substance possesses a reasonable degree of heat stability is indicated by the fact that Morgan and Fairbrother were able to heat potent solutions of euglobulin to 56 C. for one-half hour without demonstrable effect on neutralization. These experiments were not performed on a quantitative basis and are therefore but an indication that the neutralizing substance is just as thermostabile as diphtheria antitoxin.

Practically, these experiments indicate that the least total loss in antibody occurs by concentrating both the euglobulin and pseudoglobulin fractions of horse serum. It is problematic whether these findings would apply to fractionation of antiviral sheep and goat serums or to neutralizing normal or convalescent serum, since Banzhaf and Famulener [125] have shown that diphtheria antitoxin has a different relative distribution in the globulin fractions of these animals than in the horse.

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124. Banzhaf, E. J.: The Further Separation of Antitoxin from Its Associated Proteins in Horse Serum, Collected Studies, Bur. of Lab., Dept. of Health, New York City **7**:114, 1912.

125. Banzhaf, E. J., and Famulener, L. W.: The Proteins and Antitoxin in the Serum of Goats Immunized Against Diphtheria, Collected Studies, Bur. of Lab., Dept. of Health, New York City **8**:208, 1914.

## SUMMARY AND CONCLUSIONS

While conclusive evidence in favor of a filtrable virus as the etiologic agent of poliomyelitis has not been produced to the satisfaction of all, the data are overwhelmingly in favor of this assumption. Recent investigation has failed to support the view of Flexner, Noguchi and Amoss that globoid bodies, peculiar minute micro-organisms, represent the active agent. The proponents of the streptococcic etiology of the disease have not been able to marshal significant additional evidence to support their claims. On the other hand, in animal experimentation with the virus the disease has been reproduced so easily and regularly that grave doubt is cast on the irregular and questionable results obtained with the other agents.

The only practicable test of antiviral serum activity is the in vitro virus neutralization test that utilizes susceptible monkeys as indicators of the end-point of this serologic reaction. In the past many technical variations of the neutralization test have been employed, most of them without due consideration to the number of paralyzing doses of virus, and many with undue favor conferred on the serum by overwhelming volume. Recently, more standardized methods have been employed by the majority of investigators. Passive protection and treatment of the experimental disease with all types of serum have yielded irregular results that have been interpreted by many investigators as indicating evidence of an in vivo virucidal property of serum. When these results are studied in the light of the natural outcome of successful inoculation of susceptible monkeys by routes other than intracerebral, they become less impressive. Indeed, although otherwise interpreted, there is little choice between the results in large series of animals that have received serum and those that have remained without it. Thus, such results can be produced only statistically, and passive protection and serum treatment of the experimental disease are not practical tests of the activity of the serum. The most promising of these procedures are the intranasal method of introducing the virus and the so-called "therapeutic test" of Flexner and Amoss in which the virus is given intravenously. Although the former method simulates the route of infection in man, it has been shown recently that only a certain percentage of animals are susceptible to this route of inoculation; thus the results are reduced to a statistical basis. The "therapeutic test" of Flexner and Amoss has been shown to be impracticable, since the extreme sensitivity of the meninges often allows infection to occur even after a simple lumbar puncture.

It is pointed out that the origin of a sample of serum is no direct guarantee that it contains neutralizing substance. Many individual samples of human convalescent serum have been found not to contain the neutralizing substance, while "normal" human serum has been found

by certain authors to be just as potent in neutralizing substance or more so than convalescent human serum. There is a divergence of opinion concerning the content of the antistreptococcus horse serum of Rosenow and Nuzum and Willy. The production of antiviral animal serums has been shown to be practically feasible although nonsusceptible animals are used. The latter serums have been shown to have as much neutralizing substance as the average human convalescent serum. None of these serums is exclusively favored by the results of in vitro neutralization tests.

Tests of serum indicate that a period of from a few months to a year after a paralytic attack is a more feasible time to obtain potent human convalescent serum than days or weeks after the acute stage. There is also specific evidence that tends to show that persons having a mild attack of the disease with more or less complete recovery produce a more potent neutralizing serum than either those with widespread paralysis or those who have received treatment with serum. Certain authors maintain that the blood group is as important a factor as a paralytic attack of the disease. These observations relative to the acquisition of immunity in poliomyelitis need confirmation. Storage of human convalescent serum for two or three years is thought to have little effect on the concentration of the neutralizing substance. Tests of serum show the neutralizing substance to be relatively thermostabile—being able to withstand a temperature of 56 C. for one-half hour—and to be little affected by filtration through Berkefeld or Seitz filters.

Investigations on the concentration of antiviral horse serum have demonstrated the probability of some concentration of the neutralizing substance in the globulin fractions of this serum. These studies have not been applied to human convalescent serum.

# POLIOMYELITIS

## II. RESULTS OF TREATMENT IN THE ACUTE DISEASE; ANALYSIS OF REPORTS ON 4,400 PATIENTS TREATED WITH SERUM; OBSERVATIONS ON 2,660 UNTREATED PATIENTS

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In recent years the treatment of acute poliomyelitis by serums has received publicity in the medical literature. Although treatment by convalescent serum was first proposed by Netter, Gendron and Touraine [1] in 1911, the problem did not receive consideration in this country until the spectacular epidemics of 1916 in New York and New England and of 1917 in the midwestern states. Numerous brief studies on serum therapy were available at that time, but until recently,[2] there has never been data available from a sufficient number of cases to judge the results accurately. Recently authors have approached the subject by an attempt

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1. Netter, A.; Gendron, A., and Touraine: Sérotherapie de la poliomyélite antérieure aiguë, Compt. rend. Soc. de biol. **70**:625, 1911.

2. (*a*) Aycock, W. L., and Luther, E. L.: Preparalytic Poliomyelitis: Observations in One Hundred and Six Cases in Which Convalescent Serum Was Used, J. A. M. A. **91**:387 (Aug. 11) 1928. (*b*) McEachern, J. M.; Chown, B.; Bell, L. G., and McKenzie, M.: Résumé of the Results of Therapy with Convalescent Serum in Poliomyelitis, Canad. M. A. J. **20**:369, 1929. (*c*) Aycock, W. L.; Luther, E. H.; McKhann, C. F.; Smith, E. C., and Kramer, S. D.: Preparalytic Poliomyelitis: Further Observations on Treatment with Convalescent Serum, J. Infect. Dis. **45**:175, 1929. (*d*) Macnamara, J.: The Treatment of Acute Poliomyelitis by Means of Human Immune Serum, M. J. Australia **2**:838, 1929. (*e*) Lomer, T. A., and Shireff, W. T.: Report of an Epidemic of Poliomyelitis in Ottawa, 1929, Canad. M. A. J. **22**:228, 1930. (*f*) Rohmer, P.; Meyer; Phalizot; Tassovatz; Volette, and Willemin: Rapport clinique et thérapeutique sur l'epidémie de poliomyélite d'Alsace en 1930, Bull. Acad. de méd., Paris **105**:364, 1931. (*g*) Shaw, E. B.; Thelander, H. E., and Limper, M. A.: Treatment of Poliomyelitis, J. A. M. A. **97**:1620 (Nov. 28) 1931. (*h*) Park, W. H.: Therapeutic Use of Antipoliomyelitis Serum in Preparalytic Cases of Poliomyelitis, J. A. M. A. **99**:1050 (Sept. 24) 1932; New York State J. Med. **33**:91, 1933. (*i*) Laidlaw, F. W.: Poliomyelitis in the State of New York in 1931, ibid. **99**:1053 (Sept. 24) 1932. (*j*) Levinson, S. O.; McDougall, C., and Thalhimer, W.: Acute Anterior Poliomyelitis in the Chicago Area in 1931, ibid. **99**:1058 (Sept. 24) 1932. (*k*) Macnamara, J., and Morgan, F. G.: Poliomyelo-Encephalitis in Victoria (1925-1931): Treatment by Human Immune Serum, Lancet **1**:469, 1932; ibid. **1**:527, 1932.

to evaluate statistically the apparent clinical improvement that has been frequently observed in the treatment of early acute poliomyelitis. Without exception, they have adduced favorable evidence for reduction both in mortality rate and in incidence and degree of paralysis, most strikingly observed in the preparalytic form of the disease. Notwithstanding these favorable reports, there are still many skeptical observers, notably Kellogg,[3] Lichtenstein,[4] Park [2b] and Wesselhoeft.[5] Indeed, in later reports certain authors who previously favored the use of convalescent serum have denied the efficacy of serum, at least under special circumstances of age [6] and of epidemic variations.[7]

The gravity of this disease is attested by an average mortality of from 10 to 15 per cent in epidemic years. Not the least to be considered is the social disability of residual paralysis, the more severe grades of which occur in from 25 to 50 per cent of cases in certain epidemics. With these as average figures, it is not surprising that when the mortality for the group treated with serum in the preparalytic stage is reduced to the low average of 0.9 per cent and the incidence of the severely disabling forms of paralysis to 5.7 per cent,[2a] such evidence is regarded as favorable to serum treatment.

All observers agree that the outcome of both an individual case and a given epidemic is practically impossible to predict. Even when observed in retrospect, it is most difficult to set a single case into any ordered scheme which will serve as the natural history of the disease. These facts have been referred to by many authors as the "uncertainties" of the disease. It is probable that a composite of the experiences of a number of observers dealing with many, varied and scattered foci of the disease and with a large number of cases will constitute a more accurate record of the variations of this disease as affected by treatment than a single report from one locality.

Undoubtedly, the largest single experience with the serum treatment of poliomyelitis in several epidemic years has been that of the Harvard group, who are said [7] to have treated with convalescent serum more than 800 patients with preparalytic poliomyelitis. Their recorded experiences are with but 304 cases.[8] The New York City group [2b] treated alternate

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3. Kellogg, W. H.: The Present Status of Convalescent Serum Therapy, J. A. M. A. **93**:1927 (Dec. 21) 1929.

4. Lichtenstein, A.: Ueber Rekonvaleszentenserumtherapie bei Poliomyelitis acuta, Ztschr. f. Kinderh. **51**:39, 1931.

5. Wesselhoeft, C.: The Present Status of Serum Treatment in Acute Poliomyelitis, J. Pediat. **3**:330, 1933.

6. Limper, M. A.; Thelander, H. E., and Shaw, E. B.: Poliomyelitis in Adults: Report of 60 Cases, J. Prev. Med. **5**:475, 1931.

7. Footnote 2a, pt. I.

8. Footnotes 2 a and c and 7.

patients in a group of 927 in the preparalytic stage. Laidlaw [21] reported on the treatment of 764 patients in the preparalytic stage in the 1931 pandemic in the state of New York. For the purposes of this review, there have been collected from the literature the experiences of various authors with treatment in more than 4,400 cases, of which, I believe, 2,637 early cases (preparalytic and early paralytic cases combined) are available for statistical analysis. For comparison, there are available in these reports 2,660 cases observed in the same epidemics in which serum treatment was not given but which are of widely variable comparative value, owing to the diverse methods used by these authors in selecting a concurrent control group. Less value will be placed on these control groups as a measure of the effectiveness of the form of therapy under consideration than on a comparison of the results obtained by various methods of treatment or on a consideration of the results in relation to the character of the epidemic. As will be seen later, the variation in the type of epidemic has a profound influence on the apparent effectiveness of therapy in the acute stage. I am fully aware that in a consideration of this type, one does not have exactly comparable statistical units, as the data have come from many and varied sources. On the other hand, reports that deal with cases either superficially or in small numbers have been excluded from statistical consideration and are dealt with only in a general way.

Several forms of treatment have been used besides the administration of serum from persons who have passed through a definite recognized attack of paralysis, i. e., so-called convalescent serum. In this article consideration will be given to other methods of treatment, although it appears that convalescent serum has become more popular in recent years. The statement, "from both the theoretical and experimental points of view that convalescent serum may be effective in the treatment of early poliomyelitis," [7] should not be adduced solely as an argument in favor of this type of therapy, since, as has been pointed out in part I, similar and equally conclusive theoretical and experimental evidence exists in favor of at least one other type of serum, antiviral animal serum, and perhaps other types of serum.

It is noteworthy that nearly every report dealing with treatment in the acute stage of poliomyelitis has favored some one type of treatment. This fact is particularly true in the reports that deal with the results of serum therapy. Thus, Rosenow,[9] using an antistreptococcus serum, stated: "paralysis did not develop in a single instance when treatment was begun before its onset, and all recovered. No extension occurred following the giving of serum in the patients who recovered and in whom paralysis was marked at the time of the serum treatment." Aycock

9. Rosenow, E. C.: The Treatment of Epidemic Poliomyelitis with Immune Horse Serum, J. A. M. A. **69**:1074 (Sept. 29) 1917; J. Infect. Dis. **22**:379, 1918.

and Luther,[2a] finding favor for convalescent serum, wrote: "This report indicates a favorable effect of convalescent serum, when administered in the preparalytic stage of poliomyelitis, as shown by: a low mortality rate, a low average total paralysis and a strikingly low paralysis of the severer grades." According to Shaw, Thelander and Limper [2g] the antiviral animal serums that have been produced and used most recently are likewise found to be therapeutically active: "It is our conviction that the use of known highly immune serum will be productive of consistent results and that hyperimmune animal serum offers the greatest promise in this direction." In this article an attempt will be made to rationalize these equally convincing statements of the proponents of these three types of serum and to review other therapeutic attempts that have been made in the acute stage of the disease.

## VARIATIONS IN EPIDEMICS OF POLIOMYELITIS

From the earliest careful epidemiological study [10] of poliomyelitis, the fact was recognized that coincident with the occurrence of frank paralytic cases in a given community there have occurred more than the usual number of mild illnesses. It has been believed from epidemiological evidence by Wickman,[10] Draper,[11] Frost,[12] Römer [13] and Paul, Salinger and Trask [14] that those "mild illnesses" represented nonparalytic cases of poliomyelitis. A more skeptical attitude was taken by Aycock,[15] who stated: "Epidemiological evidence does not reveal the presence of any considerable number of cases of abortive type of infection. In a number of instances in which there were good opportunities for the detection of such cases, little evidence of their existence was found." Notwithstanding this opinion, Aycock and his co-workers [2e] admitted that in the 1928 epidemic in Massachusetts, they saw 143

10. Wickman, I.: Acute Poliomyelitis, Nervous and Mental Disease Monograph Series 16, New York, Nervous and Mental Disease Publishing Company, 1913.

11. Footnote 6, pt. I.

12. Frost, W. H.: Epidemiological Studies of Acute Anterior Poliomyelitis, U. S. Pub. Health Service, Hyg. Lab. Bull. no. 90, Washington, Govt. Printing Office, 1913.

13. Footnote 5a, pt. I.

14. (*a*) Paul, J. R.; Salinger, R., and Trask, J. D.: Abortive Poliomyelitis, J. A. M. A. **98**:2262 (June 25) 1932. (*b*) Paul, J. R., and Trask, J. D.: The Detection of Poliomyelitis Virus in So-Called Abortive Types of the Disease, J. Exper. Med. **56**:319, 1932. (*c*) Paul, J. R.; Salinger, R., and Trask, J. D.: Studies on the Epidemiology of Poliomyelitis: I. Methods and Criteria for the Detection of Abortive Poliomyelitis, Am. J. Hyg. **17**:587, 1933; Studies on the Epidemiology of Poliomyelitis: II. The Incidence of Abortive Types of Poliomyelitis, ibid. **17**:601, 1933; (*d*) footnote 121, pt. I.

15. Aycock, W. L.: The Epidemiology of Poliomyelitis, J. A. M. A. **87**:75 (July 10) 1926.

patients "as suspected preparalytic poliomyelitis who were ruled out" (on the combined basis of physical examination and tests of the spinal fluid), citing as justification for the elimination that "none subsequently developed paralysis." In the same epidemic, these authors were able to make a positive diagnosis of "preparalytic poliomyelitis" in 116 cases on combined evidence from clinical observation and examination of the spinal fluid. Paralysis developed in only 71 (61.2 per cent) of the latter patients. The diagnosis in the other 45 (38.8 per cent) might fairly be questioned on the basis of the criterion that these authors themselves propose, namely, the development of actual paralysis at some time. In an earlier contribution, Aycock and Luther [2a] cited 3 specific instances, which, in their opinion, should be excluded from the category of preparalytic poliomyelitis. In only 1 of these cases was incontrovertible evidence submitted that the illness was other than preparalytic (or nonparalytic) poliomyelitis. These instances are cited merely to show that many of the cases that are diagnosed as preparalytic poliomyelitis may well be nonparalytic poliomyelitis or another intercurrent illness of different etiology in which meningeal irritation has occurred.

Recent authors, considering the pathogenesis of the disease from an anatomic point of view, have expressed diametrically opposite opinions. Burrows [16] believes that involvement of the central nervous system is purely an accident occurring in a systemic disease, while Faber [17] presents strong evidence that the disease is confined to the cerebrospinal axis. The contradictory opinions of these authors result from the circular processes of deductive reasoning and not from any conflict in the basic observations from which they start.

Such facts indicate that there is an overlapping between instances of "abortive poliomyelitis," "preparalytic poliomyelitis" and "nonparalytic poliomyelitis" and cases in which mild temporary paralysis ensues. Probably all these variations of the disease play an important rôle in disseminating infection. At least, they are of paramount importance in evaluating the treatment of early poliomyelitis. The first "hump" in the dromedary phenomenon of poliomyelitis, pointed out for the disease in man by Draper [11] and for the experimental disease in monkeys by Harmon, Shaughnessy and Gordon,[18] might be considered as abortive poliomyelitis, with the second "hump" paralytic, preparalytic or nonparalytic poliomyelitis, since lumbar puncture during the first period of pyrexia consistently yields a normal spinal fluid. While these variations in reaction to infection by a single pathogenic agent have been

16. Burrows, M. T.: Is Poliomyelitis a Disease of the Lymphatic System?, Arch. Int. Med. **48**:33 (July) 1931.

17. Faber, H. K.: Acute Poliomyelitis as a Primary Disease of the Central Nervous System, Medicine **12**:83, 1933.

18. Footnote 61, pt. I.

recognized for years, it was not until recently that attempts were made to determine the numerical relationship of each of these types to one another and to the frankly paralytic type of infection. Such investigations have been approached from three points of departure: statistical, immunologic and by detection of the virus. Opinion has become crystallized in a definition of the first three types of the disease, concerning which confusion had previously existed. Aycock [2a, c] defined these types of the disease and was aware of the possible influence of such variations on the results of treatment, as were Paul, Salinger and Trask [14] in a recent consideration of abortive poliomyelitis. Harmon, Shaughnessy and Gordon [18] showed that these variations of the disease occur in experimentally inoculated monkeys but more infrequently than in the epidemic disease in man. "Abortive poliomyelitis" refers to the type of the disease characterized only by non-nervous manifestations, without alterations in the spinal fluid. "Preparalytic poliomyelitis" is a preliminary stage characterized by variable systemic manifestations, by signs of meningeal irritation and by alterations in cells or protein content (or both) of the spinal fluid. "Nonparalytic poliomyelitis" shares the same characteristics with preparalytic poliomyelitis except that this type is never followed by actual paralysis. Conceivably, "mild paralytic poliomyelitis" may follow preparalytic poliomyelitis or be but a step beyond nonparalytic poliomyelitis, since functional paralysis occurs through edema of the central nervous system without anatomic paralysis due to actual destruction of nerve cells.

Aycock [2a, c] has repeatedly stated that it is impossible to determine the relationship between preparalytic and nonparalytic poliomyelitis. Even the cases that show a mild transient weakness occupy a debatable position. This relationship has already been established on a small scale by Zingher and others (table 1). The controlled therapeutic experiment of Park [2b] contributes important data on this same question. Table 1 shows the incidence of nonparalytic among preparalytic cases, all confirmed by examination of the spinal fluid. In the first division of this table the incidence of nonparalytic among untreated preparalytic patients is presented while in the second division of the same table the number of nonparalytic cases that have been observed by a number of authors in series of cases of preparalytic poliomyelitis treated by convalescent serum is shown. The latter incidence is alleged to have been the result, in part, at least, of serum treatment in the preparalytic stage. The third division of the table lists a similar group of patients treated with Rosenow's serum. For the purposes of comparison, there is given when possible the severity of the epidemic in question in terms of the only index available, that of the fatality rate in the city or state as a whole.

It is seen from these data on 531 untreated patients that even in epidemics of average severity, a large share of patients (71.5 per cent) in whom the disease is diagnosed in the preparalytic stage by examination of the spinal fluid never become paralyzed. Further examination

TABLE 1.—*Incidence of Nonparalytic Poliomyelitis in Preparalytic Untreated (a) and Treated (b and c) Poliomyelitis*

| Author | Date of Epidemic | Number of Cases | Non-paralytic Cases | Per Cent | Population Unit, as a Whole | | |
|---|---|---|---|---|---|---|---|
| | | | | | Cases | Deaths | Fatality |
| (a) Zingher [90] | 1916 | 14 | 8 | 57 | 9,023* | 2,448 | 27.1 |
| Draper [11] | 1916 | 31 | 19 | 61 | 9,023* | 2,448 | 27.1 |
| Peabody (New England J. Med. **185**: 175, 1921) | 1920 | 13 | 9 | 69 | 696 | 144 | 20.7 |
| Lichtenstein [4] | 1929 | 20 | 11 | 55 | 121* | 20 | 16.5 |
| Park [2h] | 1931 | 408 | 301 | 74 | 4,138* | 504 | 12.2 |
| Laidlaw [21] | 1931 | 45 | 32 | 71 | 2,051‡ | 154 | 7.5 |
| Total | | 531 | 380 | 71.5 | | | |
| (b) Schwarz [114a] | 1916 | 21 | 9 | 43 | See text | ..... | 27.1 |
| Peabody [114c] | 1916 | 51 | 35 | 69 | 1,927 | 452 | 23.5 |
| Draper [11] | 1916 | 41 | 20 | 49 | See text | ..... | 27.1 |
| Amoss and Chesney [91] | 1916 | 14 | 11 | 79 | See text | ..... | 27.1 |
| Zingher [90] | 1916 | 64 | 53 | 83 | See text | ..... | 27.1 |
| Ayer [114b] | 1921-1926 | 92 | 66 | 72 | § | § | § |
| Aycock and Luther [2a] | 1927 | 106 | 37 | 35 | 1,189 | 169 | 14.2 |
| Aycock et al.[2c] | 1928 | 116 | 54 | 47 | 434 | 65 | 15.0 |
| Macnamara [2d] | 1928 | 42 | 23 | 55 | 164 | 32 | 19.5 |
| McEachern [2b] | 1928 | 74 | 69 | 93 | 434 | 49 | 11.3 |
| Shaw and Thelander [88] | 1928 | 19 | 17 | 89 | 303 | 80 | 26.4 |
| Berry (quoted by Riley: J. A. M. A. **94**: 550 [Feb. 22] 1903) | .... | 49 | 45‖ | 92 | 289 | 27 | 9.3 |
| Lomer and Shireff [2e] | 1929 | 115 | 109 | 95 | § | § | § |
| Shaw, Thelander and Limper [2g] | 1930 | 53 | 28 | 53 | 1,903 | 157 | 8.2 |
| Lichtenstein [4] | 1929 | 39 | 23 | 59 | 121 | 20 | 16.5 |
| Park [2h] | 1931 | 519 | 357 | 69 | 4,138* | 504 | 12.2 |
| Laidlaw [21] | 1931 | 764 | 593 | 78 | 2,051‡ | 154 | 7.5 |
| Levinson, McDougall and Thalhimer [2j] | 1931 | 65 | 31 | 48 | 170* | 32 | 18.8 |
| Total | | 2,244 | 1,580 | 70.4 | | | |
| (c) Rosenow [9] | 1917 | 16 | 15 | 94 | § | § | § |
| Nuzum and Willy [97] | 1917 | 14 | 13 | 93 | 535* | 187 | 34.9 |
| Sugg (J. Iowa M. Soc. **15**: 573, 1925) | 1924 | 18 | 13 | 72 | 65 | 16 | 24.6 |
| Rosenow and Nickel [38] | 1921-1925 | 232 | 188 | 81 | § | § | § |
| Rosenow [98] | 1930 | 50 | 45 | 90 | § | § | § |
| Total | | 340 | 274 | 80.6 | | | |

* Number of deaths in the city alone.
† Obtained from the following sources: Poliomyelitis from 1929 to 1931, League of Nations Monthly Epidemiological Reports, **11**: 3, 1932. Personal communication to the author from E. Hietr, Medical Officer of Health, Stockholms Stadshälsovårdsnämnd.
‡ Number of deaths in the state exclusive of New York City.
§ No comparative data available.
‖ Includes a few cases that showed mild transitory paralysis.

of this table shows that larger percentages of nonparalytic cases occur in groups of preparalytic cases only under two conditions: in a small number of cases (Amoss and Chesney, Shaw and Thelander, Nuzum and Willy, and Sugg) or in a relatively mild epidemic (McEachern, Lomer and Shireff, Rosenow and Nickel, and Rosenow). The total number of nonparalytic cases alleged to have resulted from the administration of serum (70.4 per cent of 2,244 cases) is strikingly like the incidence of nonparalytic poliomyelitis in patients untreated in the pre-

paralytic stage (71.5 per cent of 531 cases). If the history in many cases in which the diagnosis may be made in the preparalytic stage from symptoms and examination of the spinal fluid is that of nonparalytic poliomyelitis, the influence of serum in preventing paralysis, which has been intimated in all the aforementioned reports, may well be questioned. Heretofore comparisons with patients treated in the preparalytic stage have been made with those seen too late in the disease to receive treatment in this stage or with the average result in the population unit at large, usually the state. By either of these methods the possibility that many preparalytic cases may be cases of nonparalytic poliomyelitis is eliminated from consideration in the control groups. Aycock and his co-workers [2a, c] and MacEachern and his associates [2b] have met these objections with the statements that they have been able to see practically all the illnesses in the child population of the community under consideration and believe that they have not missed any considerable number of mild cases. Both of these groups of authors give a statistical probability index as to the number of cases that would have had to occur to equalize the results in treated and nontreated patients on the *a priori* assumption that serum was of no value. Neither of these arguments disposes of the implied indications of the natural outcome of the group of preparalytic cases as being largely nonparalytic cases.

Following the actual demonstration by Shaughnessy, Harmon and Gordon,[19] Aycock and Kramer [20] and others [21] that there are in the general population a number of persons who have neither been in contact with a frank case of poliomyelitis nor had the disease, but who nevertheless possess neutralizing substances against the virus of poliomyelitis in their blood stream, it has been assumed that such substances are the result of an immunizing contact with the virus, either clinical or, more probably, subclinical. Kramer and Aycock [22] investigated the inci-

19. Shaughnessy, H. J.; Harmon, P. H., and Gordon, F. B.: Neutralization of Poliomyelitis Virus by Human Serum, Proc. Soc. Exper. Biol. & Med. **27**:742, 1930; J. Prev. Med. **4**:463, 1930.

20. Footnote 115, pt. I.

21. (*a*) Fairbrother, R. W., and Brown, W. G. S.: The Action of the Serum of Normal Individuals on the Virus of Poliomyelitis, Lancet **2**:895, 1930. (*b*) Schultz, E. W., and Gebhardt, L. P.: Incidence of "Normal" Persons Possessing Demonstrable Antibodies for Poliomyelitis Virus in Their Serum, Proc. Soc. Exper. Biol. & Med. **28**:409, 1931. (*c*) Faber, H. K.: Transfusion Donors as Sources of Immune Serum for Treatment of Poliomyelitis, J. A. M. A. **96**:935 (March 21) 1931. (*d*) Hudson, N. P., and Lennette, E. H.: The Examination of Pooled Human Serum for Its Neutralizing Effect on the Poliomyelitis Virus, J. Prev. Med. **6**:335, 1932. (*e*) Footnote 72, pt. I. (*f*) Footnote 73, pt. I.

22. Kramer, S. D., and Aycock, W. L.: Abortive Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **29**:98, 1931.

dence of neutralizing substances in children from a community in which there had been cases of frank poliomyelitis and various mild illnesses and in an adjacent community where no frank poliomyelitis had occurred. They found no essential difference in the incidence of neutralizing substances in either group and concluded that the coincidental minor illnesses did not represent nonparalytic poliomyelitis. The general question has been raised as to whether the presence in the blood stream of such "immune bodies," not only against the virus of poliomyelitis but also as postulated by the failure of "normal" persons to react in the Schick and Dick tests, is a result of specific immunization or of a general serologic maturation. The investigations of Friedberger, Bock and Fürstenheim [23] on the occurrence of antisheep hemolysins, supposedly antibodies of no significance in immunity to disease, at present constitute the evidence against the belief of spontaneous immunization in these diseases.

Viewed in this light, the well known reports of Bay-Schmith [24] and of Heinbecker and Irvine-Jones [25] of an extensive antitoxic immunity against diphtheria among Eskimos, with clinical diphtheria either absent or exceedingly rare, and the reports of many authors [26] of that as high a degree of antitoxic immunity against diphtheria and scarlet fever exists among a tropical population as is present in temperate climates where such diseases are not rare, might as logically be interpreted as a concept of serologic maturation rather than subclinical immunization. The matter is still *sub judice,* with the most recent work tending against the hypothesis of immunologic maturation. Morales and Mandry [27] in Puerto Rico have just completed a most significant study of the acquisition of immunity against diphtheria in the tropics; they found that persons with a positive Schick reaction practically never acquire

23. Friedberger, E.; Bock, G., and Fürstenheim, A.: Zur Normalantikörperkurve des Menschen durch die verschiedenen Lebensalter und ihre Bedeutung für die Erklärung der Hautteste (Schick, Dick), Ztschr. f. Immunitätsforsch. u. exper. Therap. **64**:294, 1929.

24. Bay-Schmith, E.: Versuche über die Schicksche Reaktion bei Eskimos in Grönland, Klin. Wchnschr. **8**:974, 1929.

25. Heinbecker, P., and Irvine-Jones, E. I. M.: Susceptibility of Eskimos to the Common Cold and a Study of Their Natural Immunity to Diphtheria, Scarlet Fever and Bacterial Filtrates, J. Immunol. **15**:395, 1928.

26. Doull, J. A.; Ferreira, M. J., and Parreiras, D.: The Results of the Schick and Dick Tests in Rio de Janeiro, J. Prev. Med. **1**:513, 1927. Parr, L. W.; Goudale, R. H., and Krischer, H.: The Epidemiology of Diphtheria and Scarlet Fever in the Subtropics with Special Reference to the Syrian States under French Mandate, J. Prev. Med. **4**:39, 1930.

27. Garrido-Morales, E., and Mandry, O. C.: Mechanism of Natural Immunity to Diphtheria: Preliminary Report of Experiments in Porto Rico, Am. J. Hyg. **14**:89, 1931.

a negative reaction unless they become at some time carriers of virulent diphtheria bacilli. Kramer [28] was recently able to show in 6 persons the acquisition of neutralizing substances against the virus of poliomyelitis following prolonged or intimate contact with a patient in the acute stage of paralytic poliomyelitis, but not after merely casual contact in 6 other patients. Trask and Paul [29] have been successful in demonstrating an acquisition or an increase in titer of neutralizing substances against a recently isolated human strain of virus in 5 instances of abortive poliomyelitis and in 1 frank case of paralysis. A comparative test of these same serums with a passage strain of virus leaves the issue clouded. These authors attribute this clearcut experimental issue to the use of a virus freshly isolated from the same epidemic that involved the patients in question. Such a contention would agree well with the recent finding (see page 1210) that neutralization tests with a recently adapted virus strain from the same epidemic were more reliable than when these tests were performed with a monkey passage strain that had been employed for some time in the laboratory. Thus, in these last two reports the acquisition of immune principles against the poliomyelitis virus seems to be the result of direct contact with the infectious agent.

Brodie [21f] recently published a quantitative study of the largest number of nonconvalescent adult serums yet presented, which, according to him, indicates that serum from persons not having a history of contact with a frank instance of poliomyelitis has a smaller amount of neutralizing substance than serum taken after contact. However, a close study of this author's data reveals that the difference between the contact and noncontact groups is not striking and might easily have been that of chance variation. Until more convincing evidence is offered, it must be admitted that the acquisition of immunity in poliomyelitis seems to follow closely the mechanism of acquired immunity in other infectious diseases.

It has been assumed that the existing methods of inoculation of monkeys for detection of the poliomyelitis virus in the nasopharynx are unreliable in a quantitative study, since the presentation of Taylor and Amoss,[30] who were the first to detect the virus in the nasopharynx of a patient with nonparalytic poliomyelitis, gave the impression that the method was difficult and unreliable. That this is not necessarily the case and that the method deserves more confidence are indicated by the

28. Kramer, S. D.: Immunity to Poliomyelitis in the General Population, J. A. M. A. **99**:1048 (Sept. 24) 1932.

29. Footnote 121b, pt. I.

30. Taylor, E., and Amoss, H. L.: Carriage of the Virus of Poliomyelitis with Subsequent Development of the Infection, J. Exper. Med. **26**:745, 1917.

recent reports of Paul, Salinger and Trask [14] who detected the virus in the nasopharynx of 2 of 12 patients with abortive poliomyelitis. More extensive investigations of this type will define the limitations of the method of animal inoculation for detecting the virus in nasopharyngeal washings. If the method is found reliable, further application will lead to a true index of the incidence of nonparalytic poliomyelitis and may even define accurately the actual period of contagion.

It is to be expected that with the variation in the number of cases from year to year there should be some variation in the mortality rate indicating variations in the severity of the disease. In the years of greatest mortality, but few cases are reported, while in epidemic years the mortality rate is lower, as a rule. There are notable exceptions to this generalization, especially the early pandemics in this country. These facts, however, indicate in epidemic years, proportionately, a greater number of cases of mild paralysis with fewer of the rapidly advancing types of paralysis and of fulminating bulbar types, together with a possible increase of the nonparalytic and abortive types of the disease. The last-mentioned types are believed to be responsible for a great share of contagion. Thus, in epidemic years, conditions should be favorable for apparently successful serum therapy. The latter circumstances are also favorable to the diagnosis of preparalytic poliomyelitis both because the public and physicians are on the alert for the disease and because the milder types of the disease are those that present the longest period of meningeal irritation before the onset of the paralysis.[31]

In attempting to evaluate the results of any type of therapy, the type of epidemic and the number of days after the febrile onset of the disease, as well as the phase of the epidemic when treatment has been applied, should be considered in an ideal report. Mortality and possibly the severity of the paralysis vary with the phase of the epidemic curve. This fact is well illustrated by the weekly report of the fatality rate as given by the health department of New York City [32] for the 1916 pandemic in that city. At the beginning of the epidemic the fatality rate was 8 per cent. At the height of the epidemic in July and August this rate rose to 26 per cent, while in the final weeks of the epidemic, it fell to 10 to 12 per cent. The noticeable drop in the fatality rate for the past three seasons, as seen in the single or collective data for the states, possibly denotes a more benign type of infection, or it may

31. Tebbutt, A. H., and Helms, K.: A Report of the Epidemic of Poliomyelitis in New South Wales 1931-1932, M. J. Australia **20**:43, 1933.

32. Department of Health of the City of New York: The Epidemic of Poliomyelitis in New York 1916, Monograph Series no. 16, New York, 1917; Weekly Bulletin **22**:302, 1932.

only be the result of a better reporting of mild cases. To state this as a certainty, epidemic curves will have to be followed for more years in the future. The week by week fatality rates for the 1931 pandemic in New York City are illustrative of this last thesis. As stated elsewhere, this epidemic was characterized by the relatively few deaths in proportion to the number of cases reported. Weekly fatality rates did not vary to any significant degree during the course of this epidemic, averaging 12.5, 11.3, 15.1 and 12.2 per cent, respectively, for July, August, September and October of that year. Many of the reports which will be reviewed in this article do not contain enough data to make possible an analysis of the fatality rate in relationship to the curve for the epidemic.

The objections of Kellogg [8] to the use of data from a state at large as an index of the severity of the epidemic, in which he quoted reports from various counties in the state as showing extreme variations from the average rate for the state, utilize statistics that indicate poor reporting of nonfatal cases in three of four counties and that are admitted by the state department of public health to be highly unsatisfactory.[33] Further, when the monthly fatality rates for these counties are examined in place of the rate for the whole 1927 epidemic, it is seen that the monthly rates vary from one another even more than the data reported by Kellogg for these counties. When data are examined from counties in California in which reports are known to be reliable, both for 1927 and for other years, the extreme deviations within a single year of epidemic pointed out by Kellogg from inadequate data are not found.

The age of patients plays an important part in statistical evaluation, since it is a well known fact that in adolescents and adults the percentage of fulminating and severe cases is greater, although the incidence is lower. Adults are said to be more refractory to treatment with serum,[6] but there are as yet no adequately comparable data on this point. Many authors [34] agreed that the apparent response of children to serum therapy is frequently rapid but others [2h] deny that there is a difference between treated and untreated preparalytic poliomyelitis in this respect. The only report dealing with a statistical analysis of this point [35] finds a successive fatality rate of 8.2, 11.9, 20.5 and 27.9 per cent in the first four hemidecades. There might be levied the usual objection of fewer cases in the last two age groups, accounted for by the known age incidence of the disease.

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33. Personal communication to the author from Dr. G. S. Porter, Director, California Department of Public Health, San Francisco.

34. Footnotes 2 a, c, d and g, pt. 11; 6 and 97a, pt. I.

35. Footnote 97a, pt. I.

The correctness of the diagnosis probably does does not play a very important rôle in influencing the results of treatment, at least in the more recent reports,[36] as the authors cited are aware of the pitfalls in the diagnosis of preparalytic forms of the disease and have carefully excluded questionable cases. In the earlier reports one cannot be so certain that the disease in question was poliomyelitis without paralysis. With a study of the many clearcut descriptions of the possible early symptoms of acute poliomyelitis, as given by Peabody, Draper and Dochez,[37] Draper,[11] Rosenow,[38] Macnamara,[2d] Marinesco, Manicatide and Draganesco,[39] Aycock and his co-workers,[2a, c] Rohmer and others,[2f] Gordon [40] and by Brahdy and Lenarsky,[41] confirmed by examination of the spinal fluid and the outcome of the case, but few erroneous diagnoses should be made.

The statement of Aycock [2a] that "many serum treated patients thought not to have developed any paralysis were found to have considerable muscle weakness" is an indication that the proportions of cases of "no paralysis" given in other reports are not comparable on account of the lack of a detailed muscular examination as carried out by this author. From a practical point of view this criticism is more apparent than real, since it is well known that with adequate after-restraint and rest almost every patient with "muscle weakness" recovers adequate function.

The method of Aycock [2a, c] in computing average paralysis from detailed muscular examinations is commendable from the point of view of accuracy. However, in one of this author's reports,[2c] it is seen that examinations reported as comparable were made many months apart. Again the method may be criticized since certain muscles that are paramount in equilibration and joint stability are given the same numerical rating as less important muscles that either contribute little to subsequent deformity or are easily replaced or deposed by relatively simple orthopedic reconstruction. A few cases with extensive paralysis, which alone furnish no more evidence against the efficacy of treatment than the results in malignant cases of diphtheria and scarlet fever, upset the trend of a mass of data, as occurred in two of the reports of Aycock

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36. Footnotes 1, 2, 3, 4, 5 and 7.

37. Peabody, F. W.; Draper, G., and Dochez, A. R.: A Clinical Study of Acute Poliomyelitis, Rockefeller Institute for Medical Research, monogr. no. 4, 1912.

38. Footnote 9; footnote 97a.

39. Footnote 63a, pt. I.

40. Gordon, J. E.: Diagnosis of Early Poliomyelitis, J. A. M. A. **99**:1043 (Sept. 24) 1932.

41. Brahdy, M. B., and Lenarsky, M.: The Differential Diagnosis of Acute Poliomyelitis, J. A. M. A. **102**:1358 (April 28) 1934.

and his associates.[42] These presentations, though, focus on the equally important phases of paralysis in estimating disability from the disease, since death is not economically as disabling as paralysis. A universal agreement on the significance of three or four grades of disability from paralysis would be more simple and obviate the objections just raised against reporting the effects of an acute disease in terms of insignificantly slight degrees of residual paralysis.

When treatment has been applied with convalescent serum, the assumption seems implied that all such serum contains adequate amounts of a therapeutically active principle, and in many reported epidemics serum has not been tested. The results of Aycock and Kramer,[20] who in testing sixty samples of convalescent serum, found five that contained no neutralizing substances, and of Shaughnessy, Harmon and Gordon,[19] who found that one of five samples of convalescent serum obtained from investigators regularly using such serums in treatment contained no neutralizing substances, are examples of this fallacy. For such tests, quantitative estimations first employed by the latter authors should be the method of choice for assay of serum. It is encouraging to note from some of the most recent reports [43] that only tested serum has been used.

It has been stated by certain authors [44] that the method for determining the results of treatment which would eliminate most of the objections cited would be the indiscriminate selection of alternate cases. Unless a larger number of cases were considered by such a method than those cited in the majority of reports quoted in this review, it is doubtful if the significance of results would justify the experiment, since too few of each grade of severity of the disease would be included. The recent report of Park [2h] on 927 preparalytic cases fully justifies the experiment. The same method had also been used by Kramer and his associates [7] in a small number of cases. The results in the treated and nontreated series in both these reports are so nearly identical that they constitute most important documents in negating the value of convalescent serum. However, the mildness of human cases as compared with the experimental disease in monkeys has been used for years to rationalize the divergence in result between therapeutic experimentation on monkeys and treatment of the disease in man.

### ATTEMPTS AT MEDICAL THERAPY IN POLIOMYELITIS

It may be fairly stated that all the drugs that have been used with the view of modifying the pathologic processes in poliomyelitis have been unsuccessful. As a result, this field remains only experimental.

42. Footnotes 2c, pt. II; 2a, pt. I.
43. Footnotes 2 i and k, pt. II; 2a, pt. I.
44. Footnotes 2 a and k and 3.

Flexner and Clark [45] proposed the oral use of methenamine in this disease, since it was known that in addition to its being eliminated in the urine its split products were, in part, excreted into the ventricular subarachnoid space. An experimental basis was claimed in that "in a proportion of animals [monkeys] so treated [methenamine, orally], but not in all, the incubation period was prolonged and the onset of paralysis entirely prevented." There has been no experimental confirmation of these results, and the results obtained in isolated cases in man have been disappointing, although it is only fair to state that there have been no systematically studied series of cases in which this drug has been employed, even with the wide publicity that it has enjoyed. Fraser [46] used the drug orally in 22 patients, with no clearly beneficial results, and even with the development of an alarming hematuria in 2. Later, Flexner and Amoss [47] were unable to prevent nasal infection by the use of this drug, even when the medication was started several days before the inoculation of experimental monkeys.

Since it is considered that the most probable portal of entry of the virus into the body during natural infection is through the nasopharynx, a few studies have been made on the feasibility of application of certain "nasal disinfectants" in relation to the virus. Levaditi and Landsteiner [48] found, in vitro, that oil of menthol and a powder composed of menthol, phenyl salicylate and boric acid rendered the virus innocuous when the mixture was tested intracerebrally in monkeys. In another study [49] of similar tests, thymol was found not to render the virus ineffective, while certain solutions of potassium permanganate and hydrogen dioxide destroyed the virus. The practical application of these findings is uncertain, as it is known that once infection has occurred, it is impossible to modify the course of the disease by external applications. Such applications have never been found to be active in prophylaxis.

Clark [50] has reported prolongation of life and an improvement in paralytic phenomena including respiratory embarrassment in certain experimentally infected monkeys by administering epinephrine intra-

45. Flexner, S., and Clark, P. F.: Experimental Poliomyelitis in Monkeys: IX. Immunity Principles; Effect of Hexamethylenetetramine; Early Diagnosis; Virus Carriers, J. A. M. A. **56**:585 (Feb. 25) 1911.

46. Fraser, F. R.: Clinical Observations of Ninety Cases of Acute Epidemic Poliomyelitis, Am. J. M. Sc. **148**:1, 1924.

47. Footnote 78e, pt. I.

48. Footnote 78b, pt. I.

49. Levaditi, C., and Landsteiner, K.: Action exercée par le thymol, le permanganate de potasse et l' eau oxygénée sur le virus de la poliomyélite aiguë, Compt. rend. Soc. de biol. **68**:740, 1910.

50. Clark, P. F.: The Action of Subdural Injections of Epinephrin in Experimental Poliomyelitis, J. A. M. A. **59**:367 (Aug. 3) 1912.

thecally, while in certain similarly infected monkeys "there was no definite proof that life was prolonged and the symptoms were only moderately ameliorated." Fraser,[46] Lewis,[51] Hoyne and Cepelka [52] and Weisenburg [53] as well as the physicians of the New York Department of Health [32] have used epinephrine intraspinally in the acute stage of the disease in man. Meltzer,[54] on theoretical grounds, was a warm advocate of the use of this drug in acute poliomyelitis to reduce edema of the central nervous system. The results recorded by the authors cited have not been encouraging. In New York, better results were obtained in untreated patients; certain patients even reacted acutely and disadvantageously to the drug. More recently Clark [55] tested the action of ephedrine in acute experimental cases in monkeys with indifferent results. Brahdy and Scheffer [56] recently published the results of the intrathecal use of ephedrine in 10 cases. While they obtained a lower mortality rate in these 10 cases as compared with control cases, they did not draw final conclusions, but expressed the opinion that the effect of the treatment was favorable.

With the same theoretical conception of improving the symptoms due to inflammatory edema alone, Aycock and Amoss [57] studied experimentally the effect of hypertonic solutions of sodium chloride administered intravenously; they found that the injections not only reduced the volume of the brain and spinal cord but had the effect of reversing the direction of flow in the perivascular lymphatics of the central nervous system in an animal that was acutely ill. They believed that by giving convalescent serum to animals both intraspinally and intravenously in conjunction with the intravenous injection of hypertonic solution of sodium chloride, a most favorable course of the experimental disease resulted. That this method is not without danger was witnessed by the

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51. Lewis, P. M.: Report of Seventy Seven Cases of Acute Poliomyelitis Treated in the New York Throat, Nose and Lung Hospital by Intraspinal Injections of Adrenalin Chloride, M. Rec. **90**:540, 1916.

52. Hoyne, A. L., and Cepelka, F. P.: Poliomyelitis with Some Observations on Thirty Cases, J. A. M. A. **67**:666 (Aug. 26) 1916.

53. Weisenburg, T. H.: Poliomyelitis: A Study of the 1916 Philadelphia Epidemic with a Report of 717 Cases, M. Clin. North America **1**:393, 1917; J. Nerv. & Ment. Dis. **46**:443, 1917.

54. Meltzer, S. J.: The Treatment of Acute Poliomyelitis, New York M. J. **104**:337, 1916.

55. Clark, P. F.: Personal communication to the author.

56. Brahdy, M. B., and Scheffer, I. H.: The Treatment of Acute Epidemic Poliomyelitis by the Intrathecal Administration of Ephedrine, Arch. Int. Med. **45**: 102 (Jan.) 1930.

57. Aycock, W. L., and Amoss, H. L.: Experiments on Local Specific Therapy in Poliomyelitis: The Utilization of Hypertonic Solutions in the Serum Treatment of Experimental Poliomyelitis, Bull. Johns Hopkins Hosp. **34**:361, 1923.

sudden death of certain of the animals, presumably from the direct depressant effect of large quantities of the salt or its ions. Smith [58] reported marked symptomatic relief in a child with advanced respiratory malfunction with cyanosis due to acute poliomyelitis to whom 40 cc. of a 30 per cent solution of sodium chloride was given intravenously. Howe [59] stated that he had used hypertonic solutions of dextrose intravenously with resulting improvement in a large number of cases, both in the preparalytic stage and after the paralysis had developed. This treatment relieved meningeal irritation, apparently checked the progress of paralysis in some instances and accelerated the return of function. On theoretical grounds dextrose is probably a less dangerous substance than hypertonic solution of sodium chloride for dehydration of the central nervous system.

Jungeblut [60] briefly reported attempts at chemotherapeutic control of the experimental disease with a wide variety of substances including silver arsphenamine, neoarsphenamine, tryparsamide, colloidal bismuth, bismuth potassium tartrate, an organic antimony compound, mercurochrome, metaphen, plasmochin, acetylsalicylic acid, ester of chaulmoogra oil and hexylresorcinol. None of these substances was found to be active in restraining an already established infection, but partial success as a prophylactic agent was recorded with the antimony compounds, ester of chaulmoogra oil and hexylresorcinol and especially with mercurochrome. However, not enough animals were treated with any single one of these agents to make the results conclusive. Jungeblut [61] also tried ester of chaulmoogra oil in a small series of cases in New York in the 1931 pandemic, without benefit. Young, Hill and Scott [62] briefly alluded to 2 cases of acute poliomyelitis which they believed might have been favorably affected by mercurochrome. Kolmer and Rule [63] also failed to affect the course of the experimental disease by certain chemicals. There is not sufficient experimental evidence as yet to warrant any extensive trial of these substances in the disease in man.

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58. Smith, T. C.: Intravenous Injection of Hypertonic Salt Solution in Acute Poliomyelitis, Am. J. Dis. Child. **31**:360 (March) 1926.

59. Howe, H. S., quoted by Neal, J. B., in International Committee for the Study of Infantile Paralysis: Poliomyelitis, Baltimore, Williams & Wilkins Company, 1932.

60. Jungeblut, C. W.: Attempts at Chemotherapy in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **28**:176, 1930.

61. Jungeblut, C. W.: Personal communication to Neal.[59]

62. Young, H. H.; Hill, J. H., and Scott, W. W.: The Treatment of Infections and Infectious Diseases with Mercurochrome 220 Soluble, Arch. Surg. **10**:813 (May) 1925.

63. Kolmer, J. A., and Rule, A. M.: A Note on the Chemotherapy of Experimental Poliomyelitis of Monkeys, Proc. Soc. Exper. Biol. & Med. **31**:50, 1934.

Protein therapy has received some attention. Sicard, Haguenau and Wallich [64] proposed the use of autohemotherapy in acute poliomyelitis, reinjecting 10 cc. of blood intramuscularly in a series of from ten to twelve injections. In 20 cases reported, no striking improvement resulted. The previous report of Duncan [65] was apparently not known to these authors. Marinesco, Manicatide and Draganesco [39] used this method in the Roumanian epidemic of 1927, with indifferent results, which they believed to be less encouraging than those obtained with serum. Algora Nieto [66] claimed, without presenting evidence, that protein therapy used as a coadjuvant with convalescent serum gave the maximum of benefit in the acute stage. Jungeblut and Kopeloff,[67, 60] knowing of the beneficial results obtained by fever in syphilis and of the relatively low thermal death point [68] of the virus of poliomyelitis, applied fever therapy of both the infectious and noninfectious types to the experimental disease without effect on the course of the paralysis. In view of the practical experiences of Park and his associates in the pandemic of 1931 with horse serum, which will be discussed in a later section of this review, the use of foreign protein in the acute stage of this disease should be discouraged. Notwithstanding these unfavorable reports, Thenebe and Cenci [69] found, on treating 33 patients in the preparalytic stage by intramuscular injections of sterile milk, that there was a smaller incidence of paralysis in their cases than in the average series of cases in the 1931 epidemic in Massachusetts. Such a small series is not sufficient to eliminate chance selection of patients.

### IRRADIATION THERAPY IN ACUTE POLIOMYELITIS

In Europe, especially in the southern European countries, treatment of acute poliomyelitis by irradiation has become an accepted procedure. In this country but few reports on its use have appeared. Bordier [70] was the first to propose the use of roentgen rays in the treatment of poliomyelitis. Since the first recommendation of their use, he [71] has

64. Sicard, Haguenau, and Wallich, quoted in Poliomyelitis, League of Nations Monthly Epidemiological Reports **9**:97, 1930.

65. Duncan, C. H.: Autotherapy in Poliomyelitis, New York M. J. **104**:342, 1916.

66. Algora Nieto, A.: Should Protein Therapy Be Used in Treatment of Acute Anterior Poliomyelitis? Siglo méd. **86**:481, 1930.

67. Jungeblut, C. W., and Kopeloff, N.: Influence of Artificial Fever on the Course of Experimental Poliomyelitis, J. Infect. Dis. **49**:348, 1931.

68. Shaughnessy, H. J.; Harmon, P. H., and Gordon, F. B.: The Heat Resistance of the Virus of Poliomyelitis, J. Prev. Med. **4**:149, 1930.

69. Thenebe, C. L., and Cenci, V. P.: Treatment of Acute Anterior Poliomyelitis with Non-Specific Protein: A Preliminary Report, New England J. Med. **207**: 880, 1932.

70. Bordier, H.: Sur les réactions électriques d'hypothermie locale, Bull. Acad. de méd., Paris **77**:172, 1917.

71. Bordier, H.: Le nouveau traitement de la paralysie infantile, Presse méd. **32**:414, 1924.

added diathermy and galvanic stimulation, which are to be applied during both the acute stage and the stage of resolution. His recent published results [72] indicate more than the average percentage of recovery without residual paralysis. Picard [73] has reported favorably on diathermy applied to the involved spinal segments during the acute stage. All these European studies are without adequate controls, and the conclusions should be drawn with reservation. The results are not dissimilar to the average outcome of the disease.

Hyperesthesia, both cutaneous and of deep tissue, is a distressing subjective symptom seen frequently in certain epidemics of poliomyelitis. Philips and Galland [74] reported marked symptomatic relief from persistent residual pain under the influence of roentgen treatment of the spinal segments involved. The application of roentgen rays at a late date, after maximum improvement had been obtained by ordinary physical therapeutic methods, resulted in a further return of function. There were no control cases, and the report is unduly optimistic.

From an experimental point of view, the evidence concerning the effect of roentgen rays on the disease is conflicting. Amoss, Taylor and Witherbee [75, 67] reported that monkeys primarily exposed to roentgen rays were more susceptible to experimental infection than nonirradiated controls; they believed this to be a phenomenon secondary to lymphatic damage by roentgen rays. Lenz and Jungeblut [76] recently treated the experimental disease by roentgen rays and found that "monkeys treated either during the incubation period or with manifest paralytic symptoms furnish no evidence suggesting any benefit from roentgen therapy." Further, these authors found that in vitro exposure to roentgen rays failed to modify the virulence of the virus. These findings do not absolutely contradict the positive benefit that has been observed in the disease in man, since a large share of the benefit obtained in clinical cases is of subjective improvement from hyperesthesia, which cannot be evaluated in experimental animals.

### SERUM THERAPY IN ACUTE POLIOMYELITIS

An attempt will be made in this review to present by a comparative method the results that have been obtained in the treatment of preparalytic and early paralytic poliomyelitis with three types of serum: the

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72. Bordier, H.: Diathermy and Other Electrical Agents in Infantile Paralysis, Brit. J. Actinotherapy **5**:201, 1931.

73. Picard, H.: Ueber diathermische Behandlung der akuten spinalen Kinderlähmung, Monatschr. f. Kinderh. **28**:243, 1924.

74. Philips, H. B., and Galland, W. I.: Roentgen-Ray Therapy of Poliomyelitis, J. A. M. A. **82**:1847 (June 7) 1924.

75. Amoss, H. L.; Taylor, H. D., and Witherbee, W. D: Effect of Large Doses of X-Rays on the Susceptibility of the Monkey to Experimental Poliomyelitis, J Exper. Med. **29**:115, 1919.

76. Lenz, M., and Jungeblut, C. W.: Effect of X-Rays on Poliomyelitis Virus in Vivo and in Vitro, Proc. Soc. Exper. Biol. & Med. **29**:814, 1932.

antistreptococcus serum of Rosenow, convalescent and other known neutralizing serum from man and the antiviral animal serums. A review of the experimental evidence in favor of these serums has been made in part I. The method of preparation of the antistreptococcus serum has been amply described by Rosenow and Nickel.[35] The collection and preparation of human canvalescent serum has been presented by Morgan [77] and by Aycock, Luther and Kramer,[78] while the methods used in preparing the antiviral serums from animals has been described by Neustaedter and Banzhaf,[79] Pettit [80] and others.[81] All these serums are said to contain virus-neutralizing antibodies and thus their use in therapy is warranted, since a direct experimental method of testing therepeutic value is lacking.

In attempting a presentation of the results that have been reported in the literature on the use of serum in acute poliomyelitis, one is confronted with the problem of comparison of dissimilar data. Not only has each author presented results with an individual terminology, but the quantity of serum given and the method of administration have varied. Thus these technical variations are added to the highly variable course of the disease, the influence of which has already been discussed. However, the majority of authors have pushed treatment with serum to the point that they consider adequate for each individual case, so that the divergence in method of administration and amount of serum is more apparent than real. That factors other than treatment with serum influence the recovery in the period following the acute stage is granted. It is highly probable that the amount of rest allotted each patient and the completeness of orthopedic after-care have been as variable within groups of cases in certain reports as the variation between different reports, so that no further error has been introduced than already resided in the original data.

Significant disability from residual paralysis cannot be reckoned numerically wholly in terms of the number of paralyses of individual muscles because of the exceedingly important function of certain muscles and the relative insignificance of others. In place of such a method of estimating disability, that used for statistical purposes by Rosenow and Nickel [35] and by Park [2h] is preferable. Such a method involves tabulation under "slight," "moderate," and "severely" disabling residual paralysis. There should be groups for patients who did not have paralysis at any time and for those having paralysis that subsequently

77. Morgan, F. G.: Collecting Blood from Donors and Preparation of Curative Serum for Use in Poliomyelitis, Tr. Australasian Med. Congress, supp. to the M. J. Australia, 1927, p. 263.

78. Aycock, W. L.; Luther, E. H., and Kramer, S. D.: Technic of Convalescent Serum Therapy in Poliomyelitis, J. A. M. A. **92**:385 (Feb. 2) 1929.

79. Footnote 102, pt. I.

80. Footnote 106, pt. I.

81. Footnote 109, pt. I.

disappeared. Such a terminology would imply many facts that of necessity are absent in the data presented in this article: an agreement as to what constituted "slight," "moderate" and "severe" disability with residual paralysis, and the time at which examination was to be made to determine complete, and other degrees of, recovery of muscular function. For the latter I should suggest one year after the onset of the acute stage, since it is well known that by far the greater degree of recovery is made within the first year. By "slight" disability is meant minor disability that could be converted into a highly satisfactory function by a minor orthopedic procedure, such as limited transplantation of tendons or arthrodesis of the ankle or wrist. By "moderate" disability are meant cases presenting one flail joint or extensive paralysis limited to one extremity or to a weak axial skeleton, when this is unassociated with other "moderate" degrees of residual paralysis. More complicated cases than those enumerated could be relegated to the category of "severe" disability. The latter group includes persons who are likely to be economically disabled for the balance of their lives. A careful tabulation of disability under these heads, while not as absolute as numerical muscular examination, would present a more true but less ponderous picture of the outcome in a given epidemic. This view is also held by Park.[2h]

The data of several authors have been retabulated in the accompanying tables as could best be interpreted under the foregoing heads. Table 2 presents results obtained in the treatment of patients in the preparalytic stage by human convalescent serum, while table 3 gives analogous results obtained in the treatment of patients with early paralysis by convalescent serum. Table 4 gives data obtained in the treatment of patients in the preparalytic stage with Rosenow's antistreptococcus horse serum, and table 5 contains similar data on the use of the same serum in cases of early paralysis. The data available on patients treated with antiviral animal serums are not extensive enough to warrant tabulation; they will be presented separately in a later section. For purposes of reference there has been included a tabulation of the control cases used as an index of the effectiveness of treatment by each author. As stated previously, the actual effectiveness of the serum is not measured by the difference between selected treated and miscellaneous untreated patients. The data presented in the tables are self-explanatory. In tables 2, 4 and 5, it is consistently shown that the fatality rate is lower in the cases in which serum was given than in the control cases or among the whole group of reported cases for a given state and year, except in the data presented by Park,[2h] in which the difference between the treated and untreated patients is slight enough to be explained by chance variation. In table 3 the data are conflicting, so that from the information given the apparent effect of the serum is not clear. In a direct comparison of the data presented for convalescent serum from man and those presented for the antistreptococcus serum of Rosenow, there is no fundamental difference in outcome other

TABLE 2.—*Treatment of Preparalytic Poliomyelitis with Human Convalescent Serum*

TABLE 2.—*Treatment of Preparalytic Poliomyelitis with Human Convalescent Serum*

| Location and Date | Author | Number of Cases | Number of Deaths | Fatality Rate | No Paralysis | Per Cent | Paralysis That Cleared | Per Cent | Paralysis Slight But Persistent | Per Cent | Paralysis Severe | Per Cent | Observations on Control Cases |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| New York, 1916..... | Schwarz [114a]..... | 21 | 0 | 0.0 | 9 | 42.8 | ..... No data ..... | | | | | | No controls |
| Massachusetts, 1916 | Peabody [114c]..... | 51 | 5 | 9.8 | 35 | 68.6 | 5 | 9.8 | 2 | 3.9 | 4 | 7.8 | 60 patients treated in the paralytic stage; 21 (32%) deaths |
| New York City, 1916 | Draper [11]..... | 41 | 5 | 12.2 | 20 | 48.8 | 9 | 21.9 | 4 | 9.8 | 3 | 7.3 | 31 patients untreated in the paralytic stage; 19 (61.3%) never paralyzed |
| New York City, 1916 | Amoss and Chesney [91].. | 14 | 2 | 14.3 | 11 | 78.6 | Report does not consider this | | 1 | 7.1 | 0 | 0.0 | No controls available |
| New York City, 1916 | Zingher [90]..... | 64 | 1 | 1.6 | 53 | 82.8 | 5 | 7.8 | 5 | 7.8 | Included in previous column | | Compared preparalytic with early paralytic cases |
| New York, 1921-1926 | Ayer [114b]..... | 92 | 7 | 7.6 | 66 | 71.7 | 8 | 8.7 | 11 | 11.9 | Included in previous column | | No control available |
| Massachusetts, 1927 | Aycock and Luther [2a].. | 106 | 1 | 0.9 | 37 | 34.9 | No data | | 62 | 58.5 | 6 | 5.7 | "State as a whole." 1,189 cases; 14% fatality |
| Massachusetts, 1928 | Aycock et al.[2c]..... | 116 | 7 | 6.0 | 54 | 46.6 | No data | | 51 | 43.8 | 4 | 3.4 | "State as a whole," 297 cases; 55 deaths (18.5% fatality) |
| Victoria, Australia, 1928 | Macnamara [2d]..... | 42 | 1 | 2.3 | 23 | 54.7 | 13 | 30.9 | 3 | 7.1 | 2 | 4.7 | 123 patients not treated with serum; fatality, 21.6%; complete recovery, 8%; very severe paralysis, 48% |
| Manitoba, 1928..... | McEachern[2b]..... | 74 | 0 | 0.0 | 69 | 93.2 | No data | | 5 | 6.8 | Included in previous column | | 54 patients untreated; deaths, 6 (11%); residual paralysis, 34 (63%); complete recovery, only 14 (26.7%) |
| California, 1928..... | Shaw and Thelander [88] | 19 | 0 | 0.0 | 17 | 89.0 | 2 | 10.5 | 0 | 0.0 | 0 | 0.0 | 38 patients untreated; deaths, 3 (7.9%); no paralysis, 0 (0%); mild paralysis, 2 (5.3%); severe paralysis, 33 (86.8%) |
| Ottawa, 1929..... | Lomer and Shireff [2e]... | 115 | 1 | 0.9 | 109 | 94.9 | No data | | 2 | 1.7 | 3 | 2.6 | No controls |
| California, 1930..... | Shaw et al.[2g]..... | 53 | 1 | 1.9 | 28 | 52.8 | 16 | 30.2 | 7 | 13.2 | 1 | 1.9 | "State as a whole," 1,903 cases; 157 deaths (8.2%) |
| Stockholm, 1929.... | Lichtenstein [4]..... | 39 | 1 | 2.6 | 23 | 58.9 | 7 | 17.9 | 8 | 20.5 | Included in previous column | | 20 preparalytic and untreated patients; never paralyzed, 11 (55%); paralysis that cleared, 5 (25%); remained paralyzed, 4 (20%) |
| New York City, 1931 | Park [2h]..... | 519 | 20 | 3.8 | 357 | 68.8 | 40 | 7.7 | 102 | 19.6 | Included in previous column | | 408 preparalytic patients; died, 4 (0.9%); no paralysis, 301 (73.7%); weakness only, 58 (14.2%); paralysis, 45 (11%) |
| New York, 1931..... | Laidlaw [21]..... | 689 | 24 | 3.5 | 533 | 77.4 | 85 | 12.3 | 47 | 6.8 | Included in previous column | | None given; average outcome in the state, exclusive of New York City, 2,051 cases; 164 deaths (8%) |
| Chicago, 1931..... | Levinson et al.[21]..... | 65* | 3 | 4.5 | 31 | 47.7 | 20 | 30.7 | 8 | 12.3 | 3 | 4.6 | None given; average outcome in Chicago alone, 170 cases with 32 deaths (18.8%) |
| Montreal, 1931..... | Brodie [21f]..... | 41† | 2 | 4.9 | 33 | 80.5 | No data | | 2 | 4.8 | 6 | 14.6 | None given; average outcome in the Province of Quebec, 1,114 cases with 150 deaths (13.5%) |
| Totals‡..... | | 2,181 | 81 | 3.7 | 1,508 | 69.1 | 210 | 13.0 | 150 | 22.6 | 32 | 4.8 | |

* This number includes 33 patients treated with neutralizing serum from normal adults.
† This number includes 16 patients treated with neutralizing serum from normal adults.
‡ The totals are given per item; the percentages are calculated from the corresponding data.

than might be explained by a variation in data. Since recent work (p. 1182) has been practically unanimous in denying a causal relationship to the streptococcus of poliomyelitis, the alleged efficacy of the serum of Rosenow is indirect evidence against the efficacy of convalescent serum. No correlation could be established between variations in the results quoted by various authors and the current fatality rates. Individually, reports that were not tabulated favor the use of convalescent serum.

Netter's [82] experience with convalescent serum has been in sporadic cases in Paris. Largely owing to his influence, convalescent serum is used in Europe throughout the acute illness even for many days after the onset of the paralysis. He stated, without restriction, that the method is of value in preventing the further spread of paralysis, but

TABLE 3.—*Treatment of Early Paralytic Poliomyelitis with Human Convalescent Serum*

| Author | Number of Cases | Number of Deaths | Fatality Rate | Paralysis That Cleared | Per Cent | Paralysis Slight but Persistent | Per Cent | Paralysis Severe | Per Cent |
|---|---|---|---|---|---|---|---|---|---|
| Taylor [85] | 14 | 0 | 0.0 | 8 | 57.1 | 6 | 42.8 | Included in former column | |
| Amoss and Chesney [91] | 9 | 0 | 0.0 | 2 | 22.2 | 6 | 66.6 | 1 | 11.1 |
| Zingher [90] | 152 | 50 | 32.9 | 12 | 7.9 | 94 | 61.8 | Included in former column | |
| Macnamara [24] | 19 | 0 | 0.0 | 11 | 57.9 | 6 | 31.6 | 2 | 10.5 |
| Lomer and Shireff [26] | 26 | 2 | 7.7 | 0 | 0.0 | 24 | 92.3 | Degree of paralysis not stated | |
| Shaw and Thelander [88] | 24 | 5 | 20.8 | 6 | 25.0 | 7 | 29.2 | 6 | 25.0 |
| Shaw, Thelander and Limper [25] | 39 | 7 | 17.9 | 9 | 23.1 | 23 | 58.9 | | |
| McEachern et al.[10b] | 33 | 11 | 33.3 | 7 | 21.2 | 15 | 45.5 | | |
| Totals | 352 | 82 | 23.3 | 55 | 17.4 | 43 | 48.8 | 14 | 16.6 |

his impression was formed totally from clinical experience. Sophian [83] attempted to compare the efficacy of the intrathecal administration of human convalescent serum with that of normal horse serum in 4 and 2 cases, respectively. He concluded that the results from normal horse serum were no worse than those from the convalescent serum of man. Wells [84] treated 15 patients by the combined intraspinous-intravenous administration of human convalescent serum, noting only slight improvement in the 11 patients who survived. Taylor [85] treated 19 patients with

82. Netter, A.: Sérotherapie de la poliomyélite antérieure, Bull. Acad. de méd., Paris **71**:525, 1914; **74**:403, 1915; Arch. de méd. d. enf. **19**:1, 1916; Bull. et mém. Soc. méd. d. hôp. de Paris **40**:299, 1916; Le sérum d'anciens malades dans le traitement des poliomyélites, Presse méd. **38**:1169, 1930.

83. Sophian, A.: Specific Treatment of Infantile Paralysis, J. A. M. A. **67**:426 (Aug. 5) 1916.

84. Wells, C. W.: Immune Serum in the Treatment of Acute Poliomyelitis, J. A. M. A. **67**:1211 (Oct. 21) 1916.

85. Taylor, E.: Treatment of Poliomyelitis with Immune Serum, New York State J. Med. **17**:279, 1917.

TABLE 4.—*Preparalytic Poliomyelitis Treated with Rosenow's Serum*

| Location and Date | Author | Number of Cases | Number of Deaths | Fatality Rate | No Paralysis | Per Cent | Paralysis That Cleared | Per Cent | Paralysis Slight But Persistent | Per Cent | Paralysis Severe | Per Cent | Observations on Control Cases |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Iowa, 1917..... | Rosenow [9]..... | 16 | 0 | 0.0 | 15 | .... | 1 | .... | 0 | .... | 0 | ... | 23 patients untreated; 9 deaths; 35% mortality |
| Chicago, 1917..... | Nuzum and Willy [97].... | 14 | 1 | 7.1 | 13 | .... | 0 | .. . | 0 | .... | 0 | ... | 100 patients untreated; 38 deaths; 38% mortality |
| Iowa, 1924..... | Sugg (J. Iowa M. Soc. **15** : 573, 1925) | 18 | 0 | 0.0 | 13 | .... | 1 | .... | 2 | .... | 2 | ... | No control |
| Omaha, 1923..... | Clarke and Dow (J. A. M. A. **83** : 421 [Aug. 9] 1924) | 6 | 0 | 0.0 | 6 | .... | No data | | .. | .... | .. | ... | 41 patients untreated; 9 deaths; no statistics as to extent of paralysis |
| Wisconsin and Minnesota, 1921-1925.. | Rosenow and Nickel [35].. | 269<br>232 | 8<br>.. | 2.9<br>... | ..<br>188 | ....<br>81.0 | ..<br>Included in previous column | .... | ..<br>31 | ....<br>13.4 | ..<br>13 | 5.6 | 177 patients untreated; 31% with paralysis; others, 19% and 48.3%, respectively (see author's table); 82 of 278 died (29.5%) |
| Not given..... | Rosenow [98]..... | 50 | 2 | 4.0 | 45 | 90.0 | 2 | 4.0 | 1 | 2.0 | 0 | 0.0 | 39 patients untreated; 7 (17.9%) with slight paralysis; others, 4 with no paralysis (10.3%); 15 (38.4%) the latter with marked paralysis; 13 of 39 died (33.3% mortality |
| Totals*..... | | 373 | 11 | 2.9 | 280 | 83.0 | 4 | 1.2 | 34 | 11.1 | 15 | 4.4 | |

* The totals are given per item; the percentages are calculated from the corresponding data.

TABLE 5.—*Early Paralytic Poliomyelitis Treated with Rosenow's Serum*

| Location and Date | Author | Number of Cases | Number of Deaths | Fatality Rate | Paralysis That Cleared | Per Cent | Paralysis Slight But Persistent | Per Cent | Paralysis Severe | Per Cent | Observations on Control Cases |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Iowa, 1917..... | Rosenow [9]..... | 17 | 0 | 0.0 | 16 | .... | 1 | | | | |
| Chicago, 1917..... | Nuzum and Willy [97]..... | 138 | 11 | 7.9 | No data given on extent of paralysis | | | | | | 75 patients untreated; 13 deaths, i. e., 17.3% mortality (this excludes 25 of 100 showing respiratory paralysis on admission) |
| Iowa, 1918..... | Rowan [99]..... | 66 | 0 | 0.0 | No data | | .. | .... | .. | .... | 17 patients untreated; 8 died; mortality, 47% |
| Montana, 1921..... | Pease (quoted by Rosenow and Nickel [35]) | 51 | 2 | 3.9 | No data | | .. | .... | .. | .... | 27 patients untreated; 8 deaths; mortality, 29.6% |
| Montana, 1922..... | Sippy (quoted by Rosenow and Nickel [38]) | 35 | 2 | 5.7 | No data | | .. | .... | .. | .... | 7 patients untreated; 2 deaths; mortality, 28.6% |
| Iowa, 1924..... | Sugg (J. Iowa M. Soc. **15**: 573, 1925) | 19 | 0 | 0.0 | 10 | .... | 3 | .... | 5 | .... | No controls |
| Montana, 1916..... | Clarke [100]..... | 18 | 1 | 5.5 | 9 | .... | 3 | .... | 5 | .... | State as a whole, 40% mortality |
| Omaha, 1923..... | Clarke and Dow (J. A. M. A. **83**: 421 [Aug. 9] 1924) | 11 | 0 | 0.0 | 11 | .... | No data | | No data | | 41 patients; 9 deaths (untreated patients) |
| Detroit..... | Pryer and Bernbaum (quoted by Rosenow and Nickel [35]) | 28 | 4 | 14.2 | No data given concerning paralysis | | | | | | 52 patients untreated; 10 deaths; mortality 19.2% |
| Wisconsin and Minnesota, 1921-1925 | Rosenow and Nickel [35]..... | 344<br>277 | 32 | 9.3 | 109 | 38.9 | 94 | 33.9 | 74 | 25.9 | See text |
| Not given..... | Rosenow [98]..... | 53 | 4 | 7.5 | 38 | 71.7 | 11 | 20.7 | 0 | 0.0 | See text |
| Totals* | | 780 | 56 | 7.2 | 193 | 48.9 | 111 | 28.1 | 84 | 21.3 | |

* The totals are given per item; the percentages are calculated from the corresponding data.

human convalescent serum in the Vermont epidemic of 1916 and obtained an apparent arrest in the progression of paralysis in 6 instances, while 8 patients recovered completely from paralysis. He favored restriction of serum to early cases.

Watkins and McKenzie [86] attempted a comparative trial of convalescent serum and the antistreptococcus serum of Rosenow, 19 patients receiving the former serum and 30 the antistreptococcus serum; they found the latter most beneficial. Shaw, Thelander and Fleischner [87] reported that 5 patients treated with convalescent serum in the preparalytic stage recovered without paralysis. Shaw and Thelander,[88] in a later report of the treatment of 19 patients in the preparalytic stage and of 24 in the early paralytic stage by the intramuscular administration of convalescent serum, stated the method to be of benefit in the group of cases that they had selected. They believe the serum to have had markedly beneficial effects in certain of their cases as evidenced by the symptomatic improvement and the precipitous drop in temperature following the administration of serum. Scott [89] reported briefly on the use of convalescent serum in 43 patients in all stages of the acute disease. Although skeptical of the value of the serum, he stated that "marked improvement was observed in those that received the larger doses of serum."

In the first epidemic of poliomyelitis in Roumania in 1927,[89a] 19 patients received convalescent serum, while other groups received Pettit's antiviral horse serum, autohemotherapy and irradiation. The authors cited believed serum therapy to be superior to irradiation, but failed to find any one type of serum more beneficial than another. Rohmer and his associates [2f] reported on the serum treatment of 98 patients in the epidemic of 1930 in Alsace. Both Pettit's antiviral horse serum and recent and remote human convalescent serum were used. While they found little evidence of beneficial action for Pettit's serum, they believed that convalescent serum was highly beneficial. All of the reports that have just been reviewed have in common the fact that the observations recorded might as well have indicated the natural trend of the disease as been due to the effects of the serum.

Even though, from a statistical point of view, evidence for the value of the convalescent serum is not conclusive, there remains the possibility

86. Watkins, J. T., and McKenzie, E. D.: Acute Poliomyelitis with a Brief Review of the Recent Detroit Epidemic, Ann. Clin. Med. **4**:149, 1925.

87. Shaw, E. B.; Thelander, H. E., and Fleischner, E. C.: Convalescent Serum in Preparalytic Cases of Poliomyelitis: Results of Intramuscular Administration, J. A. M. A. **85**:1555 (Nov. 14) 1925.

88. Shaw, E. B., and Thelander, H. E.: Intramuscular Use of Convalescent Serum in the Treatment of Poliomyelitis, J. A. M. A. **90**:1923 (June 16) 1928.

89. Scott, A. J., in discussion on Kellogg.[8]

89a. Manticatide, M.; Bratescu, A., and Rusescu, A.: Beobachtungen betreffend die erste Kinderlähmungsepidemie in Roumanien, Ztschr. f. Kinderh. **48**:125, 1929. Footnote 63a, pt. I.

that accurate clinical observation will support the method. Almost without exception, every author who has employed convalescent serum has observed many instances of a return to normal temperature within a few hours after the administration of this serum, together with marked symptomatic improvement and apparent arrest in the progress of paralysis. Zingher [90] was less enthusiastic about individual cases: "It seemed to me that the action of serum in poliomyelitis is beneficial; that a larger number of serum treated patients of the same degree of severity had remained alive than would have without the use of serum." Amoss and Chesney [91] stated: "Fever, sometimes high, tended to fall rapidly to normal. Apparently, the best results are obtained in cases treated soon after onset of symptoms." MacEachern and his associates [2b] stated: "The immediate therapeutic value of serum . . . was an immediate drop in temperature and recovery from most of the symptoms." Macnamara [2d] wrote: "Administration of serum within twenty-four hours after paralysis . . . is usually followed by a fall in temperature and arrest of paralysis." Lomer and Shireff [2e] stated: "The rapid fall in temperature and the improvement of symptoms after serum treatment have some significance as a therapeutic diagnostic test." Shaw, Thelander and Limper [2g] stated: "To have watched these patients one by one was far more convincing than such a statistical report." Levinson, McDougall and Thalhimer [2j] stated: "Many patients treated . . . showed such a prompt and favorable response within twenty-four hours, a temperature drop to normal and complete subsidence of symptoms and signs . . . that it seemed almost specific." Such clinical opinions as these can scarcely be disregarded in an attempt to form an estimate concerning the efficacy of convalescent serum.

On the other hand, doubts have been cast even on the evidence afforded by the clinical observation of patients treated with convalescent serum. Lichtenstein [4] stated: "My results do not support the extreme optimism of the benefits of convalescent serum." The recent report of Park [2h] presenting the results of treatment of alternate cases in the 1931 New York pandemic is of such importance that it will be summarized in some detail. The pandemic of 1931, which centered chiefly in New York City and its environs, was the second largest outbreak of the disease on record in this country. The states of New York, New Jersey and Connecticut recorded together 8,281 cases in 1931, while in 1916, when the largest epidemic on record in this locality occurred, 18,230 cases were reported in these three states. An entirely comparable group of untreated patients was selected for comparison with those that were to receive serum, there being in all 927 patients. Serum was

90. Footnote 1c, pt. I.
91. Footnote 1b, pt. I.

administered by various methods in order to test the efficacy of each route, but such variations did not apparently influence the outcome. Park stated: "Not one of the pediatricians who treated these patients felt that he had seen any evidence of a curative influence of the serum." Statistically, when comparisons were made between the two groups of cases, no significant differences were observed. For instance, at the end of three weeks after the acute preparalytic stage, of 408 untreated patients 301 (73.7 per cent) had no paralysis or weakness, while of 519 patients treated with convalescent serum 357 (68.8 per cent) had no paralysis or weakness. The relative incidence of paralysis was 11.0 and 19.6 per cent, respectively. This group failed to record significant differences between the effect of treatment soon after the onset of preparalytic symptoms and that of treatment instituted days later in the preparalytic stage, a point that had been given much importance in previous reports by other writers.

Doubt had previously been thrown on the special efficacy of convalescent serum by the finding of a number of authors (p. 1190) that "normal" human serum contains neutralizing substances against the virus of poliomyelitis. Such findings logically suggested a trial of tested normal human serum in the therapeusis of the disease in man. Earlier, Zingher [90] had treated 43 patients in the New York pandemic of 1916, with about the same results in the group that had received untested normal human serum as in another group that had been treated with convalescent human serum (table 6). Levinson, McDougall and Thalhimer [2j] treated 33 of their 65 patients with tested normal human serum without finding any difference in the results. Brodie [21f] treated early stages of the disease in the Montreal epidemic of 1931 with both tested normal adult serum and convalescent serum, finding no essential difference between the two serums (table 7).

While a parallel seems thus to have been established between an apparent therapeutic effect and the neutralizing effect of serum in vitro, regardless of the origin of the human serum, the additional experiment, that is, the trial of nonneutralizing human serum in the disease, has not as yet been carried out. Since no essential difference between treated and untreated groups has been shown in recent reports, the experiment proposed could be done with impunity. It is possible that nonneutralizing human serum will have the same degree of apparent therapeutic effect.

Even though the effectiveness of treatment of the acute preparalytic state with convalescent serum is held in some doubt at present, there are authors who advocate passive protection of a supposed susceptible

child by serum. Flexner and Stewart [92] first proposed on theoretical grounds that in times of epidemic convalescent human serum be administered as a prophylactic measure in doses of 10 cc. for children and 20 cc. for adults. Davide [93] made a similar suggestion, but in addition furnished data that might be interpreted as evidence that the measure had practical prophylactic value. In two villages in Sweden, this author protected 73 persons under the age of 25 years with convalescent serum, while a group of 84 persons of similar age served as an uninoculated control group. Among the first group, but 1 case of poliomyelitis occurred while in the latter group there were 14 cases of the frank disease and several alleged "abortive" cases. The single protected patient in whom the disease developed was probably infected long before the protective inoculation was given, since the onset occurred forty hours

TABLE 6.—*Treatment of Poliomyelitis by Convalescent and Normal Human Serums (Zingher)*

| Type of Case | Serum Used in Treatment | Number of Patients Treated | Number Becoming Paralyzed | Number Recovering Without Permanent Paralysis | Number of Deaths |
|---|---|---|---|---|---|
| Preparalytic..... | Convalescent | 25 | 1 | .. | 0 |
| | Normal | 10 | 1 | .. | 1 |
| Paralytic..... | Convalescent | 88 | .. | 5 | 38 |
| | Normal | 33 | .. | 4 | 5 |

TABLE 7.—*Clinical Use of Convalescent and Normal Adult Serums (Brodie)*

| Serum | Number of Patients | No Paralysis | | Mild Paralysis | | Severe Paralysis | | Deaths | |
|---|---|---|---|---|---|---|---|---|---|
| | | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent |
| Convalescent..... | 25 | 20 | 80 | 2 | 8 | 3 | 12 | 1 | 4 |
| Selected adult..... | 16 | 13 | 81.2 | 0 | 0 | 3 | 18.8 | 1 | 6.3 |

after the prophylactic injection of serum. Moro [94] also recommended the use of convalescent serum as a prophylactic measure, stating that by this method the value of the serum could be demonstrated, while treatment of patients in the active stage had not been effective. He cited no specific results to affirm this contention. Park [95, 88] is said to have been responsible for the passive immunization of several hundred children in the area of New York City during the 1931 pandemic by

92. Flexner, S., and Stewart, F. W.: Protective Action of Convalescent Poliomyelitis Serum, J. A. M. A. **91**:383 (Aug. 11) 1928; Specific Protection and Treatment of Epidemic Poliomyelitis, New England J. Med. **199**:213, 1928.

93. Davide, A.: Le serum de convalescent dans la prophylaxie de la poliomyelite, Bull. Office Internat. d'hyg. pub. **20**:74, 1928.

94. Moro, E.: Ein Vorschlag zur Vorbeugung der epidemischen Kinderlähmung Klin. Wchnschr. **9**:2383, 1930.

95. Park, W. H.: quoted by Neal,[59] p. 217.

means of convalescent serum, normal adult blood and serum and refined antiviral horse serum. Among this number only 3 mild cases of poliomyelitis occurred. Brebner [96] protected 1,300 children in a single town during the eastern Pennsylvania epidemic of 1932, without a single frank instance of poliomyelitis occurring in the protected group, while in the remaining child populace of approximately 3,000 children, 32 additional cases of paralysis occurred. While it is difficult to evaluate the efficacy of a prophylactic agent in poliomyelitis on account of the low attack rate for the disease, these results were unique. Thus, three authors furnish encouraging data of the value of serum prophylaxis during an epidemic of poliomyelitis.

By reference to tables 4 and 5, it is seen that excellent results in the treatment of preparalytic and early paralytic poliomyelitis with Rosenow's antistreptococcus serum have been reported. These results are as good as or perhaps slightly better than those obtained with human convalescent serum as presented in tables 2 and 3. Regardless of the final decision that may be made concerning the position of streptococci in the pathogenesis of the lesions of this disease, any method that can produce practical results in therapy demands consideration. Thus, the place of the antistreptococcus serum remains much the same as on its first introduction in 1917. Practically, the following results are illustrative: Of 373 patients treated in the preparalytic stage with Rosenow's serum 278 (82.7 per cent) had no paralysis at any time, while there were but 11 (2.9 per cent) fatalities. Of 780 cases of early paralysis, there were 193 (48.9 per cent) in which paralysis totally disappeared after a time. That these data do not represent solely the curative properties of this serum is questioned in view of the average outcome of untreated preparalytic poliomyelitis (table 1).

As was the case with convalescent serum, there is evidence apart from statistical data which cannot be overlooked in making an evaluation of the alleged therapeutic activity of Rosenow's serum. In this instance, as well, one finds almost unanimity of opinion among the authors who have employed the antistreptococcus serums; they describe marked clinical improvement following the administration of serum. Rosenow [9] stated: "A prompt drop in temperature and the pulse rate occurred in nearly every instance quite irrespective of the previous duration of symptoms." Rosenow and Nickel [38] stated: "The apparently good effect of the serum as noted at the bedside was often striking." Nuzum and Willy [97] independently produced an antistreptococcus horse serum,

96. Brebner, W. B.: **Preliminary Report of the Results of the Administration of Normal Adult Serum in the Prophylaxis of Poliomyelitis During the 1932 Epidemic, footnote 59, p. 529.**

97. Nuzum, J. W., and Willy, R. G.: Specific Serum Therapy of Epidemic Poliomyelitis, J. A. M. A. **69**:1247 (Oct. 13) 1917.

with which they obtained similar results in treatment. They stated: "The serum appears to possess the power of definitely preventing the onset of paralysis. The injection of serum is followed by a critical fall in the patients' temperature . . . and usually other clinical evidence of improvement." These clinical improvements are said to be more prompt and striking when a concentrated preparation of globulin is used, according to the most recent report of Rosenow.[98] Rowan [99] said: "The differences in mortality and incapacity would seem to be attributable to the good effects of the serum." Clarke [100] stated: "Rosenow's serum is unquestionably of value in the treatment of these cases." DuBois [101] used the antistreptococcus horse serum in 2 sporadic cases. He attributed the recovery of both patients without paralysis to the therapeutic efficacy of the serum. Diveley [102] reported on treatment with Rosenow's serum after the onset of paralysis in 51 cases in the 1925 epidemic in Kansas City, Mo., but his results do not indicate an outcome divergent from that seen in many similar groups of untreated patients.

Although Pettit [80] was not the first to produce an antiviral horse serum, he was the first to recommend its use in the therapeusis of the disease in man. There are available reports of the use of Pettit's serum by Marinesco, Manicatide, Draganesco and Rosiano [103] and by Marinesco and his associates [89] in 30 cases in the Roumanian epidemic of 1927, and by Minet and Porez [104] in 5 cases. It is questionable if any beneficial influence was demonstrated in these two reports. The former group expressed the opinion that Pettit's serum gave as good results as convalescent serum, while Minet and Porez stated that they believed the serum to be active in arresting paralysis.

There has been much recent activity in the production, purification and testing of antiviral animal serums, but there is still a paucity of statistics and reports on the clinical use of these serums. Shaw, Thelan-

98. Footnote 30, pt. I.

99. Rowan, J. J., Jr.: Serum Treatment of Epidemic Poliomyelitis Occurring in Dubuque, Iowa, During the Summer of 1918, M. Rec. **96**:972, 1919.

100. Clarke, F. B.: Poliomyelitis with Special Reference to Treatment with Rosenow's Serum, California & West. Med. **22**:437, 1924.

101. DuBois, C. C.: Acute Poliomyelitis Treated with Rosenow's Serum, J. Indiana M. A. **17**:381, 1924.

102. Diveley, R. L.: Anterior Poliomyelitis: A Study of the Acute Stage with Special Reference to the Early Diagnosis and Treatment, J. Bone & Joint Surg. **11**:100, 1929.

103. Marinesco, G.; Manicatide, M.; Draganesco, S., and Rosiano: Sur le traitement de la poliomyélite aiguë (résultats obtenus pendant l'épidémie qui a sévi en Roumainie au cours de l'année 1927), Bull. Acad. d. méd., Paris **99**:81, 1928.

104. Minet, J., and Porez: Sur le traitement de la paralysie infantile par le sérum de Pettit, Echo méd. du nord **31**:575, 1927.

der and Limper [2g] used antiviral goat and sheep serum in 37 patients, of whom 19 were seen in the preparalytic stage. The results were apparently as good as those obtained with convalescent serum. Etienne [105] has reported on 13 patients treated with Pettit's serum; 11 escaped without paralysis, 1 recovered with residual paralysis, and 1 died. The results obtained by Park and his associates [106] with their concentrated and purified antiviral horse serum in 63 cases in the New York epidemic of 1931 indicate a higher fatality rate than usual. Of these 63 patients, 44 (69.8 per cent) recovered with no paralysis and 7 (11.1 per cent) died. Since the results were less desirable than those observed in untreated preparalytic poliomyelitis, and since severe and sometimes fatal reactions were observed when the serum was given intraspinally, Park was not favorably impressed with this serum. Considerable light is shed on the alleged beneficial results of heterologous serum in this disease by the reports of Sophian [83] and Silverman,[107] both of whom have treated patients with normal horse serum. All agree that this product contains no neutralizing substances. Sophian treated 10 patients by intrathecal injections of normal horse serum, and reported improvement in 5. Silverman treated 14 patients in the preparalytic stage by subarachnoid injections of normal horse serum, with the result that paralysis failed to develop in 9 (64 per cent).

Certain authors have contended that the clinical improvement that has been observed following intrathecal therapy has been in large measure due to decompression of the ventricular subarachnoid system. Montgomery and Cole [108] put this hypothesis to test in treating 26 patients in the preparalytic stage by repeated spinal puncture, without reinjections of serum of any kind. Sixteen (61.5 per cent) of these patients failed to become paralyzed. However, in view of the evidence presented in table 1, and since all but 5 of these nonparalytic patients had cell counts below 200 cells per cubic millimeter of spinal fluid, they probably had a mild nonparalytic condition. Engel and Segall [109] also advocate spinal drainage. Recently, Retan and Kubie [110] have considered poliomyelitis as one of

105. Etienne, G.: La sérothérapie antipoliomyélitique; son mode d'action et ses limites, Progrès méd. **44**:1845, 1929.

106. Park, W. H.; Weyer, E. R., and Banzhaf, E. J., quoted by Neal,[59] p. 326.

107. Silverman, A. C., in discussion on Aycock and Luther.[2a]

108. Montgomery, J. C., and Cole, W.: Spinal Drainage: Value in the Treatment of Early Poliomyelitis, J. A. M. A. **85**:890 (Sept. 19) 1925.

109. Engel, S., and Segall, S.: Zur Haüfung von Poliomyelitisfällen des Jahres 1927, Klin. Wchnschr. **7**:532, 1928.

110. Retan, G. M., and Kubie, L. S.: Forced Drainage in the Treatment of Poliomyelitis, Bull. Neurol. Inst. New York **1**:419, 1931; New York State J. Med. **31**:1378, 1931; Forced Spinal Drainage in Its Relation to Infections of the Central Nervous System, J. A. M. A. **99**:826 (Sept. 3) 1932.

the infections of the central nervous system that respond to their system of "forced spinal drainage." Briefly, if hypotonic solutions are administered intravenously and drainage from the spinal subarachnoid space is provided by a retained lumbar needle, a large amount of fluid can be washed through the central nervous system. Instead of increasing the hydration of the central nervous system, edema is actually decreased. Two cases of preparalytic poliomyelitis were reported by these authors. They overlooked the fact that the same clinical improvement has been recorded as resulting from repeated spinal puncture. The method, however, is a promising one. On the other hand, the withdrawal of cerebrospinal fluid without replacement by serum has been condemned by Webster [111] as likely to lead to further invasion of the central nervous system. Five cases of extensive paralysis were cited in the article by Macnamara [2d] in support of this hypothesis.

### TIME AND ROUTE OF ADMINISTRATION OF SERUM

No single route of administration of serum has been employed by the authors whose reports have been reviewed. The majority of writers administered serum either in part or exclusively into the lumbar subarachnoid space. Rosenow [112] stated that "horse serum has inherent toxicity" and should not be given directly into the subarachnoid space. This view received confirmation in the hands of Park and his co-workers.[106] Accordingly, Rosenow and others recommended that all such foreign serums be given either intramuscularly or intravenously, in doses of from 20 to 100 cc., depending on the severity of the symptoms. The serum is to be readministered daily if the patient does not respond. Nuzum and Willy [97] gave their antistreptococcus horse serum by the combined intraspinal-intravenous method without untoward results. Sophian [83] and Silverman,[107] who gave normal horse serum intraspinously, even believed that normal horse serum played an active rôle in preventing the occurrence and extension of paralysis. Pettit [80] recommended that his antiviral horse serum be given by the combined intravenous-intraspinal method. Experimentally, Harmon, Shaughnessy and Gordon [113] observed accelerated onsets of paralysis of the fulminating type occurring regularly in monkeys treated intrathecally with normal and convalescent heterologous serum intraspinally in poliomyelitis.

Convalescent serum has been given by every possible route, but the intraspinal method, either alone or combined with the intravenous or intramuscular route, is the most popular. Many authors have given

111. Webster, R., quoted by Macnamara.[2d]

112. Footnote 9. Footnotes 30 and 97a, pt. I.

113. Harmon, P. H.; Shaughnessy, H. J., and Gordon, F. B.: Unpublished experiments.

convalescent serum by the intramuscular method alone with as good results as by the methods mentioned previously. The earlier method employed by Netter,[82] Zingher [90] and others [114] was the administration of from 5 to 15 cc. of serum intraspinally alone. Wells [84] was the first to employ the combined intraspinous-intravenous method and to give larger doses of serum. The latter method has been employed by most recent workers. The standard dose employed has been from 10 to 20 cc. intrathecally and from 40 to 60 cc. intravenously, repeated daily as necessary. Later reports have given more emphasis to larger amounts of serum, as much as 100 cc. being given by certain authors. Shaw, Thelander and Limper [2g] and Canadian authors have used the intramuscular route alone, giving doses of from 25 to 100 cc. On sound theoretical grounds, Faber [17] insists that the intravenous administration of

TABLE 8.—*Comparison of Efficacy of Methods of Serum Administration (Park)*

| Outcome | Percentage of Cases | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of Cases | Per Cent |
| **Intraspinal Method:** | | | | | | | | |
| Intraspinal-intravenous | 70.0 | 6.7 | 6.7 | 4.4 | 7.8 | 4.4 | 90 | 100 |
| Intraspinal-intramuscular | 71.2 | 5.4 | 9.3 | 7.3 | 4.4 | 2.4 | 205 | 100 |
| Intraspinal-intravenous-intramuscular | 69.0 | 3.5 | 13.8 | 10.3 | 0.0 | 3.4 | 29 | 100 |
| Total per cent in group treated | 70.7 | 5.5 | 9.0 | 4.9 | 4.9 | 3.1 | 324 | 100 |
| **Method Other Than Intraspinal:** | | | | | | | | |
| Intravenous | 66.7 | 0.0 | 33.3 | 0.0 | 0.0 | 0.0 | 6 | 100 |
| Intramuscular | 61.9 | 16.6 | 8.3 | 6.0 | 1.2 | 6.0 | 84 | 100 |
| Intravenous-intramuscular | 69.8 | 6.4 | 9.5 | 6.3 | 3.2 | 4.8 | 63 | 100 |
| Total of group not treated intraspinally | 65.3 | 11.8 | 9.8 | 5.9 | 2.0 | 5.2 | 153 | 100 |

serum is the only method by which antibodies can be brought with certainty into intimate contact with the virus within the central nervous system. This author believes that only by the use of massive doses of antibody, as might be available in blood transfusion from healthy adults having neutralizing substances, will the maximum of benefit be obtained. Park,[2h] in his important contribution, made a comparison of the results obtained by different methods of administration of serum; he came to the conclusion that the results do not differ when varied methods are used. His comparative table has been reproduced (table 8).

Practically every author who has recently emphasized treatment in the preparalytic stage agrees that serum should be administered at the

114. (*a*) Schwarz, H., in discussion in Section on Pediatrics, New York Academy of Medicine, Arch. Pediat. **33**:859, 1916. (*b*) Ayer, W. O.: Poliomyelitis: Its Preparalytic Period with Results of Serum Therapy, Am. J. M. Sc. **177**:540, 1929. (*c*) Footnote 1a, pt. I. (*d*) Footnote 83.

earliest possible moment. One discordant view is that of Draper,[115] who believes that there is but one brief period in the evolution of the disease when serum is of maximum benefit. He stated: "The brief period of time between the moment of choroid plexus penetration and the moment of virus-cell union is the precious period during which the serum can be expected to neutralize the invading virus and so prevent paralysis." Apparently, this author has modified his views since an earlier publication,[11] in which he stated: "If the serum is regularly withheld until invasion of the meninges takes place, there may well be loss of valuable time." The latter view is conventional. In certain more recent publications, notably those of Aycock and Luther,[2a] and of Aycock and others,[2c] there are data demonstrating the efficacy of an earlier introduction of serum. Park [2h] has not been able to confirm this finding in a large number of cases.

### EFFECT OF AGE ON THE OUTCOME OF POLIOMYELITIS

Until recently, no particular emphasis has been placed on the special conditions of age, except the classic observation that the occurrence of the disease beyond the third hemidecade was uncommon and beyond the fourth hemidecade rare. It has been held that when the disease occurs in persons over 20 years of age, paralysis was likely to be more extensive than in patients in the first decade of life. The effect of age on mortality in this disease has been given little attention, only Rosenow and Nickel [35] having furnished data on this point. That age might be a factor in apparent response to treatment was not questioned until the recent article of Limper, Thelander and Shaw,[6] who reported 60 cases in patients over 16 years of age, occurring in the epidemic of 1930 in San Francisco. These authors state: "On the whole, results from therapy in this group of older patients were very discouraging." There is no indication in the results of others that adults respond to treatment differently from children. In fact, the reports that have tabulated cases according to age have recorded that adults seem to have escaped without paralysis even more frequently than children. It appears that another factor may be present rather than that treatment is signally a failure among adults. I have, therefore, examined statistics that indicate fatality trends in various age groups (table 9). It is seen that the fatality rate in the age groups beyond 15 years is greater than that in any hemidecade before this age, for both epidemic and endemic poliomyelitis. This fact is true regardless of the application of treatment, so that the phenomenon of increased fatality in adults is probably a part of the natural history of the disease.

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115. Draper, G.: Significant Problems in Acute Anterior Poliomyelitis, J. A. M. A. **97**:1139 (Oct. 17) 1931.

TABLE 9.—*Effect of Age on Mortality from Acute Poliomyelitis*

| Author | Type | Epidemic | Age Groups: 0 to 4 Years — Number of Cases | 0 to 4 Years — Deaths: Number | 0 to 4 Years — Deaths: Per Cent | 5 to 9 Years — Number of Cases | 5 to 9 Years — Deaths: Number | 5 to 9 Years — Deaths: Per Cent | 10 to 14 Years — Number of Cases | 10 to 14 Years — Deaths: Number | 10 to 14 Years — Deaths: Per Cent | 15 Years or Older — Number of Cases | 15 Years or Older — Deaths: Number | 15 Years or Older — Deaths: Per Cent | All Ages — Number of Cases | All Ages — Deaths: Number | All Ages — Deaths: Per Cent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nicoll (New York State J. Med. **17**: 270, 1917) | Patients not treated with serum | New York State, 1916 | 8,317* | 2,362 | 28.4 | 2,319 | 601 | 25.9 | 531 | 138 | 26.0 | 515 | 212 | 41.1 | 11,682 | 3,313 | 29.2 |
| Rosenow and Nickel [35] (part I, p. 31) | Treated with Rosenow's serum | Minnesota and Wisconsin, 1921-1925 | 440* | 36 | 8.2 | 326 | 39 | 11.9 | 161 | 33 | 20.5 | 186 | 52 | 27.9 | 1,113 | 160 | 14.3 |
| | Untreated | Minnesota and Wisconsin, 1921-1925 | 149* | 29 | 19.4 | 58 | 18 | 31.0 | 36 | 16 | 45.7 | 36 | 19 | 52.7 | 278 | 82 | 29.5 |
| Seventh and Ninth Biennial Reports of Minnesota State Board of Health, 1916-1917 and 1920-1921 | Untreated, paralyzed | Minnesota, 1916 | 397* | 37 | 9.6 | 161 | 21 | 13.0 | 79 | 20 | 25.3 | 104 | 27 | 26.0 | 741 | 105 | 14.2 |
| | Untreated | Minnesota, 1917-1920 | 161 | 28 | 17.4 | 87 | 16 | 18.4 | 32 | 6 | 18.8 | 44 | 10 | 25.0 | 313 | 66 | 21.1 |
| | Untreated | Minnesota, 1921 | 172 | 28 | 16.3 | 157 | 19 | 12.1 | 106 | 19 | 17.9 | 120 | 36 | 30.0 | 702 | 102 | 14.5 |
| California State Board of Health [33] | Endemic poliomyelitis | California, 1924 | 90 | 15 | 16.6 | † | .. | .... | 70 | 10 | 14.3 | 17 | 9 | 52.9 | 192 | 34 | 17.7 |
| | Epidemic poliomyelitis | California, 1925 | 326 | 53 | 16.3 | † | .. | .... | 360 | 63 | 17.5 | 123 | 28 | 22.7 | 821 | 144 | 17.5 |
| | Endemic | California, 1926 | 101 | 17 | 16.8 | † | .. | .... | 54 | 7 | 12.9 | 32 | 6 | 18.8 | 187 | 30 | 16.0 |
| | Epidemic | California, 1927 | 441 | 59 | 13.4 | † | .. | .... | 629 | 106 | 16.8 | 232 | 59 | 25.4 | 1,298 | 224 | 17.3 |
| | Endemic | California, 1928-1929 | ... | .. | .... | ... | .. | .... | ... | .. | .... | ... | .. | .... | 474 | 126 | |
| | Epidemic | California, 1930 | 457 | 39 | 8.6 | 646 | 31 | 4.8 | 327 | 23 | 7.0 | 441 | 64 | 14.5 | 1,903 | 157 | 8.2 |
| | Endemic | California, 1931 | 78 | 18 | 23.1 | 105 | 10 | 9.5 | 50 | 7 | 14.0 | 57 | 15 | 26.3 | 292 | 50 | 16.4 |
| Limper, Thelander and Shaw [6] | Epidemic | San Francisco, 1930 | ‡ | .. | .... | ‡ | .. | ... | 196 | 8 | 4.1 | 72 | 19 | 26.4 | 268 | 27 | 10.1 |

* Age groups 0 to 5; 6 to 10; 11 to 15, and over 16 years.
† Age groups 5 to 9 and 10 to 14; statistics are not individually available for these years; the figures in 10 to 14 year column include both groups.
‡ Age groups 0 to 14 years, inclusive, given in 10 to 14 year age column.

There are not available at this time enough data to determine accurately if there is an influence of age on the severity of paralysis. The limited data available indicate that the more severe grades of paralysis have a tendency to occur in the first decade of life. For example, in the tabulation of muscular examinations of 161 treated and untreated patients made by Aycock and his co-workers [2c] with but 2 exceptions all the moderate and severe grades of paralysis fell exclusively within the first decade. In this report 22 of the 161 patients (13.6 per cent) were beyond the age of 15 years, while 5 of the 15 deaths (33.3 per cent) occurred in the same group. Of the 17 surviving among the 22 patients beyond the age of 15, 10 or 58.8 per cent escaped without paralysis and only 3, or 17.7 per cent, had paralysis of moderate or advanced degree. Of the group below the age of 15 years, 27 of 129 patients who survived (20.9 per cent) had moderate or advanced paralysis. At present, there are no data available measuring the effect of age on the possibility of recovery from extensive paralysis.

### SPINAL FLUID CELL COUNT AND PROGNOSIS

Those who have had experience with preparalytic poliomyelitis believe with Aycock and his co-workers [2c] that "none of the findings in the preparalytic stage give any indication of the subsequent development of paralysis." There have been a few attempts to establish a means of prognosis by using the spinal fluid cell count as an index of the severity of the infection of the central nervous system. Such a proposal involves as a premise an assumption that "severe infections" of the central nervous system are of the paralytic type. That this is not wholly true is witnessed by at least one group of cases, the bulbar type, in which a rapid and fulminating onset is accompanied by little skeletal muscular paralysis but in which death from respiratory failure often follows.

Draper [11] was the first to note that patients with widespread paralysis often show the higher cell counts. He recognized exceptions: "It does not follow absolutely that cases with a low cell count do not develop paralysis." The general trend of opinion since that date has been confirmatory, but some believe that so many exceptions have been noted as to make such a prognosis valueless. Aycock and Luther [2a] state that "there is no striking relationship" between the height of the cell count and the subsequent onset of paralysis. Shaw, Thelander and Limper [2g] recorded lower average cell counts in the unparalyzed and transiently paralyzed patients than in the persistently paralyzed groups, with a still higher count in a fatal case. Laidlaw [21] recently stated: "Counts under 50 cells per cubic millimeter appear to indicate a more favorable prognosis both as to fatality and to recovery without loss of function." Since these divergent views have been expressed, I have attempted to reexam-

ine this question. The cell counts of the spinal fluid of 685 patients in the preparalytic stage have been tabulated; this information, added to the summaries given by Rosenow and Nickel [35] of 155 cases, and by Laidlaw [21] of 706 cases, makes available data for 1,546 patients in the preparalytic stage. While it is true that the average of the cell counts of the spinal fluid for patients that were never paralyzed is lower than the average for paralyzed patients, which, in turn, is lower than the average cell count in fatal cases, such differences are not striking. Indeed, when one scrutinizes individual cases, as I was able to do in the compilation mentioned, it is impossible to establish any orderly sequence that will serve as a basis for a prognosis, even when the examination of the spinal fluid is made within from twenty-four to thirty-six hours after the onset of the disease.

### TREATMENT OF RESPIRATORY PARALYSIS IN POLIOMYELITIS

Many of the deaths that occur from acute poliomyelitis are due to failure of the muscles of respiration, through involvement of the respiratory center and the centers for the spinal innervation of the muscles of respiration. Within recent years a method and apparatus have been devised by Drinker and his co-workers [116] to furnish artificial respiration by negative pressure over a long period of time. The assumption that retrogression of edema and reparative changes are possible in the motor neurons responsible for respiration was soon shown to be valid. As yet there are but few reports which give an estimate of the ultimate value of the method. Shambaugh, Harrison and Farrell [117] reported the recovery of 1 of 3 patients treated over long periods with the respirator. Shaw, Thelander and Limper [118] used the respirator on 15 patients exhibiting dyspnea during the course of acute poliomyelitis. Of these, 9 showed intercostal paralysis alone, 1 had diaphragmatic paralysis and 5 had respiratory failure due to bulbar involvement. Death occurred in all of the latter group, but among the 10 patients of the two former groups, 3 with intercostal paralysis died. Brahdy and Lenarsky [119]

116. Drinker, P., and McKhann, C. F.: The Use of a New Apparatus for the Prolonged Administration of Artificial Respiration; A Fatal Case of Poliomyelitis, J. A. M. A. **92**:1658 (May 18) 1929. Drinker, P.; Shaughnessy, T. S., and Murphy, D. P.: The Drinker Respirator, J. A. M. A. **95**:1249 (Oct. 25) 1930.

117. Shambaugh, G. E., Jr.; Harrison, W. G., Jr., and Farrell, J. I.: Treatment of the Respiratory Paralysis of Poliomyelitis in a Respiratory Chamber, J. A. M. A. **94**:1371 (May 3) 1930.

118. Shaw, E. B.; Thelander, H. E., and Limper, M. A.: Respiratory Failure in Poliomyelitis: Its Treatment with the Drinker Respirator: Report of Cases, California & West. Med. **35**:5, 1931.

119. Brahdy, M. B., and Lenarsky, quoted by Neal,[59] p. 242. Treatment of Respiratory Failure in Acute Epidemic Poliomyelitis, Am. J. Dis. Child. **46**:705 (Oct.) 1933.

treated 46 patients with the respirator in the New York pandemic of 1931. Twelve of these cases were of the bulbar type of the disease, all having a fatal outcome. Of 34 patients exhibiting chiefly intercostal paralysis, 16 (47.1 per cent) died during the course of the treatment, but 18 were discharged from the hospital in good condition. Favill and Fentress [120] reported successful treatment in an almost hopeless case. Legg [121] has extended the use of the respirator to exercising the thoracic musculature in the after-care of poliomyelitis patients. The method is now a recognized addition to the therapy of acute poliomyelitis.

## SUMMARY AND CONCLUSIONS

An attempt has been made in this review to compile and present in one place the experiences of numerous investigators who have treated acute epidemic poliomyelitis, emphasizing results that have been obtained with various types of serums. I have analyzed reports of 4,400 cases in which the patients were treated with serums and compared these with 2,660 cases in which no such treatment was given, the two series occurring coincidentally. Of the treated patients, 2,637 were seen early in the disease, the majority being in the preparalytic stage. It has been pointed out again that evaluation of the influence of a therapeutic agent in this disease especially must be a detailed and complex analysis, which will include variable factors that have been largely ignored until the past few years. The presentation of results should be standardized and extended to include even the rate and extent of recovery of muscular function in the reparative stage, since it is not inconceivable that serum or other agents may have an indirect influence even at such a remote date. I have proposed a standard scheme for the estimation of results and have attempted to transfer partially the results of others to the terms of this system. The limitations of this presentation are those imposed by the data available.

Since there is about equal experimental evidence in favor of all four types of serum that have been used, namely, the antistreptococcus horse serum (Rosenow and Nuzum and Willy), the antiviral animal serums (Pettit and others) and both convalescent and "normal" human serum, only the results that have been actually obtained in clinical trial of these serums can settle the question of the supremacy of one type.

Early diagnosis and treatment have been held as imperative for success in the serum treatment of this disease. The uncertainty of the course of the earliest type of poliomyelitis, the preparalytic stage, has

120. Favill, J., and Fentress, T. L.: A Case of Respiratory Paralysis in Poliomyelitis Successfully Treated in a Respirator, J. A. M. A. **97**:1464 (Nov. 14) 1931.

121. Legg, A. T.: The Use of the Drinker Respirator in the After-Care of Infantile Paralysis, J. A. M. A. **100**:647 (March 4) 1933.

been responsible for the apparently brilliant results when treatment has been applied in this stage. The explanation for apparently favorable results when treatment is applied in the preparalytic stage is probably the fact that many cases regarded as preparalytic are in reality non-paralytic poliomyelitis. I have collected the statistics on the fate of 531 untreated patients with preparalytic poliomyelitis; these show that 380 or 71.5 per cent never had paralysis at any time. The outcome in patients treated in the preparalytic stage does not differ from the average for untreated patients. Recent therapeutic experiments in which convalescent serum was given to alternate patients by Kramer and his associates and by Park support the same contention, showing no difference in the average outcome in treated and untreated patients.

It has again been pointed out that the nature of the epidemic, the point on the epidemic curve when treatment was applied, the age of the patient and the type and degree of orthopedic after-care are all factors of extreme importance in estimating the effect of any program of treatment. In the past these factors have been frequently ignored.

Notwithstanding the total failure of statistical presentations to favor certain types of serums, clinical observations that have been almost universally made of rapid symptomatic response to the administration of serum by an immediate drop in temperature and marked improvement in symptoms cannot be totally disregarded. All other forms of therapy in this disease have been a signal failure, with the possible exception of spinal drainage. Chemotherapy, medicinal therapy and artificial fever have all been tried without benefit. More data are needed before it can be said conclusively that serum of any of the four types is totally without value. There appears to be enough evidence from clinical observation to warrant the continued use of serums in early stages of acute poliomyelitis.

# THE BLOOD PROTEINS OF CHILDREN

## THE DISTRIBUTION OF TOTAL NITROGEN IN WHOLE BLOOD, RED BLOOD CELLS AND SERUM PROTEINS FROM THE SAME SPECIMEN

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During the last decade a number of articles have appeared on the nonprotein nitrogen constituents of the blood. The normal and pathologic limitations have been well established. With the possible exception of the albumin and globulin of the blood serum and plasma, extensive studies of the protein constituents of the blood are not commonly reported in the literature, possibly because of the difficult and time consuming methods of analysis, the absence of well defined normal values and the recognition of pathologic variations. During an investigation of the blood proteins in hypertension [1] we were stimulated to extend the study to a group of children, and we report in part the results of such observations on the nitrogen distribution of the blood of children.

### METHOD

Five-tenths cubic centimeter of oxalated whole blood (taken by venipuncture before breakfast and after a twelve hour fast) was diluted to 10 cc. with distilled water; 1 cc. portions of the mixture were used for the determination of the total nitrogen.

The separation of red blood cells and serum proteins from a definite amount of blood was made with hypertonic sodium sulphate tungstate solution, as suggested by Folin.[2] To a 15 cc. centrifuge tube 1 cc. of oxalated blood was transferred, and 8 cc. of sodium sulphate tungstate solution was added. The contents were mixed by inverting the tube, and the mixture was allowed to stand for ten minutes, after which it was centrifugated for thirty minutes at 1,500 revolutions a minute. The supernatant fluid should be as clear as water and the red cells packed on the bottom of the tube. The clear supernatant fluid was decanted into a clean 15 cc. centrifuge tube. The red cells were washed with 2 cc. of the hypertonic

From the A. Jacobi Division for Children and the Achelis Laboratory, Lenox Hill Hospital.

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2. Folin, O.: J. Biol. Chem. **86**:173, 1930.

sodium sulphate tungstate solution by gentle agitation, and the mixture was centrifugated again. The wash fluid was removed and combined with the first supernatant liquid, and 1 cc. of two-thirds-normal sulphuric acid was added; the contents were mixed and then centrifugated for from ten to fifteen minutes. The supernatant fluid was decanted.

The white sediment obtained represented the serum proteins. The packed red blood cells were dissolved in distilled water and made up to 10 cc.; 1 cc. portions were used for the determination of the total nitrogen. The white sediment of the serum proteins was dissolved in from 2 to 3 drops of 10 per cent sodium hydroxide, and when the solution was complete the volume was adjusted to exactly 10 cc. The total nitrogen value was determined on portions measuring 1 cc.

The estimations of total nitrogen were done in duplicate by a slightly modified Kjeldahl procedure with 300 cc. Kjeldahl flasks. Digestion, carried out by potassium sulphate, a pinch of powdered copper sulphate and 5 cc. of nitrogen-free sulphuric acid, proceeded for sixty minutes. When the mixture was cool, 60 cc. of water, a pinch of powdered pumice stone and 50 cc. of 40 per cent sodium hydroxide were added. The ammonia was distilled off in a Kjeldahl distillation apparatus and the distillate collected in a 100 cc. volumetric flask containing 10 cc. of distilled water and 2 drops of 10 per cent hydrochloric acid. When distillation was completed, 20 cc. of diluted Nessler's reagent was added to the flask, and the volume was made up to 100 cc. with water. The solution was compared in the colorimeter with a standard solution of ammonium sulphate (5 cc. equaling 1 mg. of nitrogen). This is a simple standardized routine procedure and may be readily varied to meet the requirements of any particular condition. The error of the method is about 1 per cent.

## RESULTS

The distribution of the total nitrogen in the whole blood, red blood cells and serum proteins from the same specimen was studied in forty-eight children, varying in age from 5 months to 13 years. These observations are recorded in the table. The diets of the children included almost every type from bottle feeding to a high caloric intake. Neither the type of diet nor the age of the patient had any appreciable effect on the distribution of the total nitrogen.

*Normal Condition.*—All subjects studied who were without fever and who were free from renal, cardiac or metabolic disturbances were considered to be normal. In this group of twenty-six normal subjects the total nitrogen level of the whole blood varied between 3,190 and 1,890 mg. per hundred cubic centimeters of blood, the average being 2,572 mg. In nine normal adults the total nitrogen level of the whole blood varied between 3,480 and 2,700 mg., the average being 3,035 mg. On the basis of these figures it appears that the total nitrogen level of the whole blood is lower in children than in adults. The total nitrogen value of the red cells in 100 cc. of blood varied between 2,530 and 1,290 mg., with an average of 1,865 mg. These figures are considerably lower than those for adults, for whom the high value is 2,880 mg., the low 2,100 mg. and the average 2,430 mg.

*Distribution of Total Nitrogen in the Blood*

| Case | Age | Whole Blood, Mg. per 100 Cc. | Red Cells | | Serum Proteins | | Diagnosis |
|---|---|---|---|---|---|---|---|
| | | | Mg. per 100 Cc. | Per Cent | Mg. per 100 Cc. | Per Cent | |
| 26866 | 12 years | 2,550 | 1,830 | 71.7 | 710 | 27.8 | Acute bronchitis |
| 34050 | 8 years | 2,730 | 2,080 | 76.1 | 660 | 24.1 | Acute pharyngitis; rheumatism |
| 26287 | 7 months | 2,360 | 1,710 | 72.4 | 630 | 26.6 | Acute pharyngitis; rhinitis |
| 32558 | 4 years | 2,640 | 1,720 | 65.1 | 900 | 34.6 | Acute pharyngitis; bronchitis |
| 33721 | 2½ years | 2,810 | 2,150 | 76.5 | 660 | 23.4 | Acute pharyngitis; rhinitis |
| 33664 | 4½ years | 2,500 | 1,800 | 72.0 | 700 | 28.0 | Acute pharyngitis; rhinitis |
| 33183 | 9 years | 3,190 | 2,400 | 75.2 | 790 | 24.7 | Acute otitis media |
| 35117 | 9 years | 2,490 | 1,790 | 71.8 | 700 | 28.0 | Acute pharyngitis; rhinitis |
| 33673 | 4 years | 2,880 | 2,080 | 72.2 | 790 | 27.4 | Acute pharyngitis; rhinitis |
| 33048 | 23 months | 2,100 | 1,470 | 70.0 | 630 | 30.0 | Acute pharyngitis; rhinitis |
| 33447 | 6 years | 2,760 | 2,140 | 77.5 | 640 | 23.2 | Acute pharyngitis |
| 33264 | 7 years | 2,560 | 1,820 | 71.0 | 750 | 29.2 | Acute pharyngitis; rhinitis |
| 32612 | 1½ years | 1,890 | 1,290 | 68.2 | 700 | 37.0 | Acute mastoiditis |
| 33570 | 2 years | 2,130 | 1,500 | 70.4 | 610 | 28.6 | Acute pharyngitis; rhinitis |
| 33526 | 8 years | 2,480 | 1,640 | 66.1 | 840 | 33.8 | Acute submaxillary lymphadenitis |
| 21434 | 10 years | 2,200 | 1,620 | 73.6 | 600 | 27.2 | Acute pharyngitis; rhinitis |
| 32151 | 12 years | 2,580 | 1,780 | 69.0 | 790 | 30.6 | Acute pharyngitis; rhinitis |
| 29543 | 7 years | 2,500 | 1,820 | 70.2 | 750 | 28.9 | Acute tonsillitis 3/18/32 |
| | | 2,560 | 1,920 | 75.0 | 640 | 25.0 | 6/29/32 |
| 36104 | 8 months | 2,200 | 1,500 | 68.1 | 680 | 30.9 | Rickets; malnutrition; anemia (secondary) |
| 35374 | 7 years | 2,980 | 2,120 | 71.1 | 840 | 28.2 | Malnutrition |
| 33116 | 13 years | 2,680 | 2,000 | 74.6 | 680 | 25.3 | Malnutrition; anxiety neurosis |
| 33922 | 8 years | 2,490 | 1,820 | 73.0 | 670 | 26.9 | Malnutrition |
| 19878 | 7 years | 2,350 | 1,640 | 69.8 | 710 | 30.2 | Malnutrition |
| 34068 | 10 years | 2,310 | 1,580 | 68.4 | 730 | 31.6 | Acute rheumatic endocarditis |
| 30767 | 11 years | 2,250 | 1,570 | 69.7 | 690 | 30.6 | Acute rheumatic fever; mitral stenosis |
| 823 | 12 years | 2,080 | 1,350 | 64.9 | 730 | 35.0 | Chronic rheumatic fever; mitral stenosis |
| 35246 | 11 years | 2,900 | 2,200 | 75.8 | 680 | 23.4 | Mitral stenosis; insufficiency |
| D3535 | 12 years | 2,620 | 2,020 | 77.0 | 600 | 22.9 | Mitral insufficiency |
| 33156 | 5 years | 2,220 | 1,520 | 68.4 | 890 | 40.0 | Rheumatic endocarditis |
| 32192 | 12 years | 2,760 | 2,140 | 80.1 | 640 | 23.2 | Chorea (mild) |
| 16052 | 13 years | 2,740 | 2,140 | 78.8 | 600 | 22.0 | Chorea (mild) |
| 14158 | 6 years | 2,320 | 1,680 | 72.4 | 650 | 28.0 | Bronchopneumonia |
| 32685 | 8 years | 2,580 | 1,930 | 74.8 | 650 | 25.1 | Bronchopneumonia; abscess of lung |
| 33451 | 6 years | 2,530 | 1,830 | 72.3 | 690 | 27.2 | Lobar pneumonia |
| 35143 | 1½ years | 2,530 | 1,900 | 75.1 | 680 | 22.9 | Bronchopneumonia |
| 34890 | 9 months | 2,250 | 1,710 | 76.0 | 540 | 24.0 | Acute pharyngitis; bronchopneumonia |
| 30802 | 17 months | 2,200 | 1,330 | 60.4 | 850 | 39.0 | Acute pharyngitis; cervical adenitis; acute nephritis |
| 26747 | 6 years | 2,550 | 1,720 | 67.4 | 820 | 32.1 | Acute nephritis |
| 30092 | 4 years | 2,664 | 1,673 | 62.8 | 952 | 35.7 | Acute nephritis; hypertension 1/9/32 |
| | | 2,320 | 1,730 | 74.5 | 590 | 25.4 | 6/16/32 |
| | | 2,350 | 1,730 | 73.6 | 630 | 26.8 | 10/10/32 |
| | | 2,860 | 2,200 | 76.9 | 630 | 22.0 | 3/8/33 |
| 33609 | 6 years | 970 | 320 | 33.0 | 490 | 50.5 | Acute nephritis; chronic myocarditis; anemia; hemoglobin 15% |
| 67970 | 10 years | 2,060 | 1,460 | 70.8 | 590 | 28.8 | Previous case of nephrosis (follow up) 2/2/32 |
| | | 2,270 | 1,730 | 76.2 | 540 | 23.7 | 10/13/32 |
| 33908 | 9 years | 2,480 | 1,860 | 75.0 | 620 | 25.0 | Purpura haemorrhagica; acute nephritis, 6/10/32 |
| | | 2,780 | 2,090 | 75.1 | 670 | 24.1 | 9/9/32 |
| 33723 | 10½ years | 2,270 | 1,640 | 72.2 | 630 | 27.7 | Pyelitis |
| 10566 | 10 years | 2,710 | 1,980 | 73.0 | 720 | 26.5 | Pyelitis; obesity; hypertension |
| 33468 | 4½ years | 2,520 | 1,680 | 66.6 | 840 | 33.3 | Unknown |
| 36299 | 5 months | 3,080 | 2,530 | 82.1 | 550 | 17.8 | Torticollis; mild rickets |
| 33151 | 9 years | 2,710 | 2,030 | 74.9 | 690 | 25.4 | Cellulitis of the left leg |
| 32693 | 11 years | 2,820 | 1,850 | 65.6 | 800 | 28.3 | Chronic appendicitis; chronic mesenteric lymphadenitis |

The total nitrogen of the red cells probably represents the nitrogen from the hemoglobin, and would therefore be less in children than in adults because of the actual differences in the hemoglobin of the blood of adults and children. If one calculates the grams of hemoglobin by multiplying the average nitrogen value of the red cells by 6.25 (the factor commonly used for the conversion of total nitrogen into protein) one obtains a hemoglobin value of 11.65 Gm. for children and 15.18 Gm. for adults. On the assumption that 15.6 Gm. of hemoglobin is normal for adults, the hemoglobin for children would be 75 per cent and for adults 95 per cent. In children the total nitrogen of the red cells ranged between 82.1 and 65.1 per cent of the total nitrogen of the whole blood, the average being 73 per cent, while in adults this relationship varied between 83 and 75 per cent, with an average of 80 per cent.

In the serum proteins from 100 cc. of whole blood the nitrogen concentration was found to be between 900 and 550 mg., the average being 701 mg. These values are much higher than those found in adults, in whom the serum proteins vary between 700 and 530 mg., the average being 591 mg. The percentage of the total nitrogen of the whole blood in the form of serum proteins varies between 34.6 and 17.8, the average being 27 per cent, while in adults the percentage varies between 25 and 17, the average being 19 per cent. In children the serum protein levels of the blood and the percentage of this fraction of the whole blood are definitely higher than in adults.

*Endocarditis.*—In six cases of endocarditis, including rheumatic fever, the total nitrogen of the whole blood varied between 2,900 and 2,080 mg., with an average of 2,397 mg., which is somewhat higher than the value for normal children. The nitrogen level of the red cells was also lower than normal, the variation being between 2,200 and 1,350 mg., with an average of 1,706 mg. The percentage of the total nitrogen of the whole blood as red cells varied between 77 and 64.9, as compared with 82.1 and 65.1 per cent for the normal group, although the average variation showed a difference of only 2 per cent. The serum protein levels varied only slightly from the normal, the highest being 890 mg. and the lowest 600 mg., with an average of 720 mg. However, the percentage of the total nitrogen of the whole blood was between 40 and 22.9, which is higher than normal.

*Pneumonia.*—Five cases of pneumonia showed a change in the total nitrogen value of the whole blood, the concentration varying between 2,580 and 2,250 mg., the average being 2,442 mg. The changes in the red cells were not significant as compared with the normal values whereas the serum protein levels were lower than normal, varying between 690 and 540 mg., with the average 642 mg. There was no change from the normal level in the percentage of the total nitrogen in terms of serum proteins.

*Nephritis.*—With the exception of case 33,609, the nine cases of nephritis, including hypertension, showed practically no changes in the total nitrogen value of the whole blood, red cells or serum proteins, as compared with the normal level. In case 33,609, showing severe acute nephritis and marked anemia, the hemoglobin was 15 per cent, the red cell count 860,000 and the blood urea nitrogen 166 mg. This case also revealed the lowest concentration of total nitrogen of the whole blood encountered in all the cases studied: 970 mg. per hundred cubic centimeters. The total nitrogen value of the red cells was very low (obviously owing to the severe anemia), being 320 mg. or 33 per cent of the total nitrogen of the whole blood. The serum protein level was also very low, 490 mg.

*Malnutrition and Rickets.*—Four children with malnutrition and one with rickets did not reveal significant changes from normal levels.

## CONCLUSIONS AND SUMMARY

1. A simple procedure is described for the determination of the total nitrogen of the whole blood, of the red cells and of the serum proteins from the same specimen of blood.

2. In normal children the total nitrogen level of the whole blood varies between 3,190 and 1,890 mg. per hundred cubic centimeters with an average of 2,572 mg.

3. The total nitrogen level of the whole blood of children is lower than that of adults.

4. The total nitrogen of the red cells from 100 cc. of the blood of normal children is between 2,530 and 1,290 mg. with an average of 1,865.

5. The total nitrogen level of the red cells and its percentage of the total nitrogen of the whole blood from which the cells are obtained are lower in children than in adults. This is due to the actual differences in the hemoglobin content of the blood of children and adults.

6. The total nitrogen of the serum proteins of the blood of normal children varies between 900 and 550 mg.; the average is 701 mg.

7. The total nitrogen level of the serum proteins of the blood of normal children is higher than that of adults.

8. In one case of severe nephritis and marked anemia the total nitrogen of the whole blood, red cells and serum proteins was markedly decreased.

9. Among the pathologic cases studied changes were noted in endocarditis and penumonia, but the small number of such cases under observation precludes the drawing of any definite conclusions.

# VITAMIN A AND COLDS

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That experimental animals which have been deprived of vitamin A are highly susceptible to respiratory infections has been demonstrated by scores of research workers. The lack of this vitamin in the dietary of man has also been observed to result in similar types of infections, including the common cold.[1]

The recent studies of Green, Pindar, Davis and Mellanby [2] indicated that concentrates of vitamin A have a therapeutic value in the treatment of certain infections, for example, puerperal sepsis. Their reports as to the value of the vitamin as a prophylactic agent against infections are also convincing. McCarrison attributed the comparative freedom from respiratory infections among certain Indian tribes to the adequacy of their dietary in vitamin A. In marked contrast to these Indians, the tribes whose diets showed a definite lack of vitamin A generally suffered from respiratory infections.

Recent experimental work has shown the relation between vitamin A and carotene, the yellow pigment found in many foods.[3] This pigment is converted into vitamin A in the liver. Experiments by Mellanby [4] and Green showed that carotene has the same effect on growth and the

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From the Departments of Nutrition and Biochemistry, College of Medical Evangelists.

1. Block, C. E.: Further Clinical Investigations into the Diseases Arising in Consequence of a Deficiency in Fat-Soluble A Factor, Am. J. Dis. Child. **28**:659 (Dec.) 1924. Cramer, W.: Vitamin A and Infections, Lancet **1**:1153 (May 24) 1930. McCarrison, R.: Some Surgical Aspects of Faulty Nutrition, ibid. **1**:1158 (May 23) 1931.

2. Green, H. N.; Pindar, D.; Davis, G., and Mellanby, E.: Diet as a Prophylactic Agent Against Puerperal Sepsis, with Special Reference to Vitamin A as an Antiinfective Agent, Brit. M. J. **2**:595 (Oct. 3) 1931.

3. Moore, T.: Vitamin A and Carotene, Biochem. J. **25**:275, 1931.

4. Mellanby, E.: Diseases Produced and Prevented by Certain Food Constituents, J. A. M. A. **96**:325 (Jan. 31) 1931.

same antiinfective action as has vitamin A. The Society for Improving the Condition of the Poor in New York, in collaboration with Professor Sherman, of Columbia University, made a quantitative determination of vitamin A in a variety of foods; no differentiation was made between the active vitamin A, found in cod liver oil or butter fat, and its precursor, carotene, found in certain green leaves and plants.

The purpose of our experiments was to determine whether supplementing the diet of school children with haliver oil or definitely enhancing it with vitamin A as found in foods would decrease the incidence and severity of colds.

## METHOD

Two groups of twenty-five children each were selected, the children ranging from 6 to 14 years of age. They were paired as nearly as possible as to age, sex, nutrition and susceptibility to colds. The members of group I were given daily one capsule of haliver oil (plain) containing at least 8,500 units of vitamin A. An additional five children were given 10 drops of haliver oil representing about 10,000 units of vitamin A. The occurrence of colds in the group was reported weekly by the mothers of the children. The severity and duration of the infections were also included in the report.

The members of group II were placed on a diet so selected as to incorporate the foods that would supply an abundance of vitamin A. The standard daily requirement was placed at 10,000 units to compare favorably with the number of units received from the daily dose of haliver oil. A few children had difficulty in reaching the standard, the range of intake being from 6,000 to 12,000 units daily. Personal visits were made to the mothers in this group to give careful instruction concerning the program of feeding. Mimeographed copies of the table of approximate units of vitamin A per ounce in most of the common foods were provided. To illustrate, spinach has 1,400 units per ounce (28 Gm.); a serving of ¼ cup, or 2 ounces (56.7 Gm.) has 2,800 units. Milk has 65 units per ounce. One cup, or 8 ounces (227 Gm.), has 520 units. Sheets specially ruled for recording the kind and quantity of food with the estimated units of vitamin A eaten by the child each meal were supplied. The reports were turned in weekly, with the report of any incidence of colds as outlined for group I.

A control group of twenty-five children was also selected. The history of this group, however, showed a much higher degree of resistance to colds than did the other two groups. Since it was the natural desire of the parents to place the children who were most subject to colds in an experimental group in which they were most likely to be benefited, only a few children possessing a marked susceptibility remained for the control group.

The experiment continued over a period of twelve weeks, beginning Nov. 20, 1932. At its close, a questionnaire was filled out by each mother. The questionnaires aided in checking the weekly reports and in determining the parents'

estimate of the benefit received. All of the children were weighed and measured at the beginning and at the close of the experiment.

The experimental results are given in the table.

*Data on Experiments with Children*

| | Children Receiving Haliver Oil | Children Receiving Vitamin A Foods | Control Group |
|---|---|---|---|
| Number of children reporting | 28 | 19 | 22 |
| Number previously susceptible to colds | 21 (75%) | 13 (69%) | 3 (14%) |
| Number with history of colds generally severe | 11 (39%) | 8 (42%) | 2 (10%) |
| Number with history of colds of long duration | 17 (60%) | 7 (36%) | 2 (10%) |
| Colds for each child during experimental period | 1.5 | 1.6 | 1.6 |
| School days missed by each child because of colds during experimental period | 2.0 | 1.26 | 2.95 |
| School days missed by each child because of colds during preliminary period | 2.4 | 2.0 | 1.2 |
| Reporting colds less severe than before | 53% | 36% | |
| Reporting colds less prolonged | 46% | 27% | |
| Average gain in weight for each child per week | 0.23 lb. | 0.24 lb. | 0.15 lb. |

## COMMENT

The experiment was planned to cover the time of year when children generally have the greatest number of colds. Results show that the control group, whose history showed the highest degree of resistance, had as many colds and missed more days of school during the experimental period than did either of the other two groups.

Previous susceptibility was based on the number of days of school missed by each child because of colds during the twelve week period just previous to the experimental period and on the reports of frequent colds supplied by the parents. Judging from these figures, the group receiving haliver oil had previous to this experiment twice the susceptibility to colds that the control group had, and the group receiving foods containing vitamin A almost the same amount. Since the number of absences from school on account of cold in the control group during the experimental period was twice that during the preliminary period, and since the absences in the group receiving haliver oil were lessened by one sixth, and the absences in the group receiving foods containing vitamin A by three eighths, it appears that the administration of vitamin A increased the resistance to between two and three times what it was.

The difference in average gain in weight for each child during one week (50 per cent more in groups I and II than in the control group) is another indication of the benefit of the feeding of vitamin A to general health and growth.

In group II the beneficial effects were most apparent among those whose intake of vitamin A was greater, with possibly two exceptions. When the diets in these two cases were checked, they were found to be definitely lacking in the foods containing vitamin C. The children who

had included liberal amounts of milk and greens, generally spinach, in their diet showed a satisfactory gain in growth and increased resistance to colds. The production of a good healthy color was decidedly noticeable in many cases.

There were three children in the control group who had no colds during either period. It was interesting to discover that in each case the children had been observing a balanced diet, which included an abundance of spinach, carrots and tomatoes.

Sherman and Cammack [5] produced the evidence that vitamin A is stored in large quantities in the body, and that the maximum quantity which the body is capable of storing is reached by gradual accumulation. A rapid storage of the maximum amount is not possible. Sherman also stated that this stored surplus actively increases the ability of the body to resist disease.[6] The degree of resistance to infections may then be measured by the relative amount of this reserve storage of vitamin A in the body. The time for maximum storage is doubtless more than twelve weeks, and we could not expect to reach the highest degree of resistance in our experiments. Other factors are also involved; for example, the diet of children up to 3 years of age has an influence on their resistance to infections which occur later in life.[7] The variation in the hygienic practices in the homes was another influencing factor that could not be entirely controlled. However, the results obtained warrant our making the following conclusions:

## CONCLUSIONS

1. Haliver oil or a balanced diet including an abundance of foods containing vitamin A plays a definite rôle in decreasing the incidence and severity of colds among school children.

2. Increased resistance is accompanied by a higher degree of general health, as is shown by an increase in weight.

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5. Sherman, H. C., and Cammack, M. L.: A Quantitative Study of the Storage of Vitamin A, J. Biol. Chem. **68**:69 (April) 1926.

6. Sherman, H. C.: Chemistry of Food and Nutrition, New York, The Macmillan Company, 1932.

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# DIMENSIONS AND GROWTH OF THE PALATE IN INFANTS WITH GROSS MALDEVELOPMENT OF THE UPPER LIP AND PALATE

## FURTHER INVESTIGATIONS

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A study of the dimensions and growth of the palate in infants with gross maldevelopment of the lip and palate has previously been reported.[1] Included in that report are twenty-eight sets of measurements of twenty-six infants. The present report includes those data and additional measurements, which are given in table 1. The additional measurements were obtained in the manner described in the previous report. The data on the normal palate are the same as in the previous report.

The method of analysis is slightly different; that is, regression lines were fitted by the correlation technic instead of by two simultaneous equations, as in the former study.[2] In general the results have not been materially changed by including data on twenty-three additional cases. The data for boys and girls are not analyzed separately in this report, since it was demonstrated in the former report that there was no significant sex difference in the relation of measurements of the head to total body length.

Regression lines were computed for each of the following measurements in centimeters on the normal and abnormal palates with crown-heel length: height of the palate, length of the alveolar process, actual width of the surface and widest tranverse diameter of the palate. A regression line was also computed for the width of the cleft in the abnormal palates with crown-heel length, in centimeters. All the regression lines and a spot diagram of the individual data for each measurement are given in the figure. The constants for each of the regression lines are given in tables 2 and 3. The results of a comparison of the means and the coefficients of regression are also given in these tables.

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From the Department of Surgery, University of Minnesota.

1. Peyton, W. T.: The Dimensions and Growth of the Palate in the Normal Infant and in the Infant with Gross Maldevelopment of the Upper Lip and Palate, Arch. Surg. **22**:704 (May) 1931.

2. This analysis of data was done under the direction of Dr. Edith Boyd of the Institute of Child Welfare and the department of anatomy of the University of Minnesota.

TABLE 1.—*Dimensions of the Palate in Infants with Gross Maldevelopment of the Lip and Palate*

| Crown-Heel Length, Cm. | Age, Days | Weight, Gm. | Fronto-Occipital Diameter, Cm. | Widest Transverse Diameter of Palate, Cm. | Actual Surface Width of Palate, Cm. | Height of Palate, Cm. | Length of Alveolar Process, Cm. | Width of Cleft, Cm. |
|---|---|---|---|---|---|---|---|---|
| | | | Boys (Maldeveloped) | | | | | |
| 51.2 | 34 | 3,380 | 12.8 | 3.67 | 3.60 | 1.20 | 2.79 | 1.42 |
| 54.0 | 20 | 3,665 | 12.3 | 3.42 | 3.56 | 1.09 | 2.94 | 1.08 |
| 54.0 | 30 | 4,215 | 13.4 | 3.80 | 3.47 | 1.20 | 3.00 | 1.45 |
| 55.0 | 18 | 3,620 | .... | 3.94 | 3.62 | 1.13 | 2.71 | 1.64 |
| 55.3 | 63 | 3,635 | 13.0 | 3.50 | 3.20 | 1.28 | .... | 1.55 |
| 57.6 | 76 | 5,158 | 12.3 | 3.75 | 3.68 | 1.14 | 2.97 | 1.31 |
| 58.5 | 48 | 5,510 | 13.5 | 3.92 | 4.15 | 1.41 | 2.97 | 1.43 |
| 58.5 | 67 | 5,410 | 14.0 | 3.92 | 3.67 | 1.23 | 2.93 | 1.51 |
| 58.7 | 64 | 4,155 | 13.3 | 3.58 | 3.31 | 1.08 | 2.84 | 1.27 |
| 66.4 | 278 | 5,895 | 14.8 | 3.39 | 4.19 | 1.14 | 2.34 | .... |
| 67.6 | 218 | 7,255 | 13.8 | 3.44 | 4.20 | 1.21 | 2.57 | 1.14 |
| | | | Girls (Maldeveloped) | | | | | |
| 50.9 | 13 | 2,865 | 11.7 | 3.49 | 3.91 | 1.20 | 2.64 | 0.98 |
| 50.9 | 13 | 2,865 | 11.7 | 3.23 | 3.68 | 1.26 | 2.77 | 0.97 |
| 53.0 | 52 | 3,650 | 15.5 | 3.26 | 3.72 | 1.27 | 2.49 | 1.25 |
| 53.6 | 71 | 3,860 | 12.2 | 3.60 | 3.63 | 1.21 | 2.56 | 1.34 |
| 53.7 | 43 | 3,865 | 12.5 | 3.63 | 3.42 | 1.16 | 2.78 | 1.60 |
| 56.6 | 52 | 4,185 | 12.5 | 3.72 | 3.61 | 0.96 | 3.20 | 1.37 |
| 56.7 | 47 | 4,400 | 12.7 | 3.69 | 3.62 | 1.31 | 2.50 | 1.34 |
| 57.5 | 95 | 4,450 | 14.3 | 3.61 | 3.65 | 1.14 | 3.00 | 1.37 |
| 57.8 | 78 | 4,640 | 13.2 | 3.45 | 3.39 | 1.23 | 2.83 | 1.22 |
| 60.5 | 148 | 4,805 | 12.8 | 3.21 | 3.21 | 0.99 | 2.80 | 1.18 |
| 67.2 | 225 | 6,349 | 12.7 | 3.81 | 3.68 | 1.06 | 2.97 | 1.04 |
| 70.5 | 380 | 81,647 | 15.2 | .... | 3.65 | 1.14 | 3.10 | 1.03 |

TABLE 2.—*Comparison of the Means of Palate Dimensions for the Normal and the Maldeveloped Palate* *

| | Cases | n | $y \pm \sigma y$ | Diff. $\pm$ S.E. | R. | P. |
|---|---|---|---|---|---|---|
| Widest transverse diameter of the palate | N (91)<br>M (50) | 1.8461<br>3.2742 | $3.34 \pm 0.0282$<br>$3.70 \pm 0.0452$ | $-0.36 \pm 0.0533$ | 6.7544 | 0.00 |
| Actual surface width of the palate | N (91)<br>M (51) | 2.3417<br>2.7480 | $3.98 \pm 0.0275$<br>$3.71 \pm 0.0370$ | $+0.27 \pm 0.0461$ | 5.8568 | 0.00 |
| Height of the palate..... | N (91)<br>M (51) | 0.6240<br>0.8762 | $0.93 \pm 0.0103$<br>$1.19 \pm 0.0204$ | $-0.26 \pm 0.0228$ | 11.4040 | 0.00 |
| Length of the alveolar process | N (91)<br>M (50) | 1.8044<br>2.5414 | $3.15 \pm 0.0271$<br>$2.98 \pm 0.0348$ | $+0.17 \pm 0.0441$ | 3.8549 | 0.00 |
| Width of the cleft..... | M(49) | 1.9001 | $1.27 \pm 0.0338$ | | | |

* N signifies normal palate; M, maldeveloped palate.

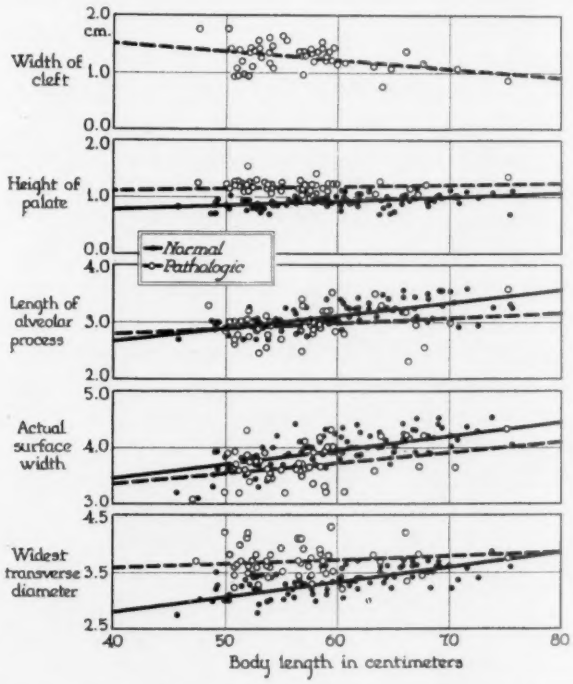
TABLE 3.—*Comparison of the Coefficients of Regression of Palate Dimensions and Crown-Heel Length for the Normal and the Maldeveloped Palate*

| | Cases | $b \pm \sigma b$ | Diff. $\pm$ S.E. | R. | P. |
|---|---|---|---|---|---|
| Widest transverse diameter of the palate | N (91)<br>M (50) | $0.024936 \pm 0.003220$<br>$0.007533 \pm 0.008534$ | $+0.017403 \pm 0.0091$ | 1.9124 | 0.057 |
| Actual surface width of the palate | N (91)<br>M (51) | $0.027346 \pm 0.002842$<br>$0.016936 \pm 0.006171$ | $+0.010410 \pm 0.0068$ | 1.5309 | 0.128 |
| Height of the palate..... | N (91)<br>M (51) | $0.005108 \pm 0.001427$<br>$0.005524 \pm 0.003571$ | $-0.000416 \pm 0.0039$ | $-0.1067$ | 0.910 |
| Length of the alveolar process | N (91)<br>M (50) | $0.022460 \pm 0.003236$<br>$0.007718 \pm 0.004853$ | $+0.014742 \pm 0.0058$ | 2.5417 | 0.012 |
| Width of the cleft..... | M (49) | $-0.011136 \pm 0.005877$ | | | |

* N signifies normal palate; M, maldeveloped palate.

SUMMARY AND CONCLUSIONS

The width of the cleft diminished with an increase in the crown-heel length. In the interval between 49 and 75 cm. in crown-heel length (first year of extra-uterine life) this decrease is approximately 4 mm. The formula for the regression line for this measure with crown-heel length is $y = 1.900 - 0.0111\,L$. The formula for the line of trend in the previous study was $y = 2.622 - 0.018\,L$. In the previous study and in the formulas presented here y and L represent the measurement of




Scattergram and regression lines of palatal measurements with crown-heel length.

the palate under consideration and the crown-heel length, respectively, in centimeters.

The cleft palate is definitely higher than the noncleft palate; they both increase with the body length. No significant difference is demonstrated between the coefficient of regression, which means that they both increase at essentially the same rate. The formula for the height of the cleft palate is $y = 0.876 + 0.005\,L$. In the previous study it was $y = 1.221 - 0.0002\,L$.

The alveolar process of the noncleft palate is demonstrated to be slightly yet significantly longer than that of the cleft palate, and comparison of the regression coefficients demonstrates that it increases in

length more rapidly. These are differences which were suggested but not definitely determined in the previous analysis. The formula for the length of the alveolar process in the cleft palate is $y = 2.541 + 0.008$ L. In the previous study it was $y = 1.824 + 0.023$ L.

The surface width is demonstrated to be slightly but significantly greater in the noncleft palate, and comparison of the regression coefficients shows that it increases more rapidly. This difference was indicated but not conclusively demonstrated in the previous analysis. The formula for the surface width of the cleft palate is $y = 2.748 + 0.017$ L. In the previous study it was $y = 1.905 + 0.033$ L.

The transverse diameter of the cleft palate is demonstrated to be wider than the transverse diameter of the normal palate, but comparison of the regression coefficients demonstrates that it increases in width much more slowly than does the normal palate. These findings are similar to those of the previous analysis. The formula for the widest transverse diameter of the cleft palate is $y = 3.274 + 0.007$ L. In the previous study it was $y = 3.799 - 0.0001$ L.

# CHOREA TREATED WITH PHENYLETHYL-HYDANTOIN AND TYPHOID VACCINE

## A COMPARATIVE STUDY

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In order to clarify, if possible, the present status of the treatment of chorea, I made a comparative study of forty-seven patients, some of whom were treated with phenylethyl-hydantoin and some with typhoid-paratyphoid vaccine.

During recent years it has been noted that chorea showed improvement when treated with phenylethyl-hydantoin and typhoid vaccine. The reports of treatment with phenylethyl-hydantoin have been encouraging, with few exceptions. Chorea has improved to such an extent with this drug that it is regarded as the treatment of choice. However, there are certain limitations and dangers in this form of treatment which I shall consider in this article.

In 1931, Dr. Lucy Porter Sutton [1] used typhoid-paratyphoid vaccine to treat chorea. At that time the end-results were regarded as better than those obtained when phenylethyl-hydantoin was used. The duration of the illness was shortened considerably, and the outlook for cure was regarded as encouraging.

In investigating the relative merits of these treatments, I collected data on twenty-four patients treated with phenylethyl-hydantoin and twenty-three treated with typhoid-paratyphoid vaccine. Since the present therapy is based on the hypothesis that fever is the factor in improvement, it was deemed advisable to study some of the chemical changes resulting from these preparations and determine whether these changes were operative in the improvement of the condition. Observation of the chemical changes was carried on to a greater extent on the patients treated with typhoid-paratyphoid vaccine.

In this series only severe cases were observed. Patients with conditions characterized as severe showed hypotonia, pseudoparalysis and inability to speak, sit up or perform voluntary acts. Those with conditions classified as moderately severe showed choreiform movements of the extremities, trunk and face, some disturbances of speech and inability to feed themselves. The milder types were not included in this observation.

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From the department of pediatrics of the Cumberland Hospital.

Dr. Thurman B. Givan, director of the pediatric division, and Dr. A. Cheron, resident pediatrician, rendered assistance in this work.

1. Sutton, L. P.: Treatment of Chorea by Induction of Fever: Preliminary Report, J. A. M. A. **97**:299 (Aug. 1) 1931.

Details of the composition and general use of phenylethyl-hydantoin may be found in many articles covering the subject thoroughly. It is my intention to discuss only those points in which the results of treatment with this drug may differ from results already reported, thus to some extent avoiding unnecessary recapitulation.

### RESULTS OF TREATMENT WITH PHENYLETHYL-HYDANTOIN

Practically all physicians who have used phenylethyl-hydantoin agree that it is of most value in well marked cases of chorea. In a disease that shows such variable changes in its course it is difficult to determine a definite line of demarcation between success and failure of treatment. The course of the disease is supposedly limited to from six to ten weeks. It was therefore deemed advisable to consider patients who were free from any choreic manifestations within less than six weeks as cured. Those with any residual signs were not regarded as cured. Steadiness of the handclasp was usually the final sign of cure. For the twenty-four patients treated with phenylethyl-hydantoin the average duration of the disease was twenty-four and a half days.

*Rash.*—From seven to eleven days after treatment was begun a rash appeared on the body, usually occurring first on the elbows, buttocks and back. However, there was no definite order of onset. The eruption was usually macular, morbilliform and discrete and sometimes became confluent in parts. Scarlatiniform and urticarial rashes were noted in two cases. Cases 7 and 11 were entirely refractory to the drug. It was noted that when the rash was intense it was followed by desquamation. In the majority of cases headache, malaise and conjunctivitis accompanied the reaction. Less frequently, edema of the eyelids, adenitis and vomiting occurred.

*Fever.*—The temperature ranged from 99 to 106 F. The average temperature for the twenty-four cases was 104.6 F. Two patients did not react. The pulse rate varied proportionately with the degree of pyrexia.

*Blood Picture.*—From 1 to 13 per cent of eosinophils frequently occurred. In eleven cases there was a depression of the white count. Leukopenia became obvious as treatment progressed; for example, in cases 10 and 21, the white count decreased to 5,200 and 5,400, respectively. As has been stated, two patients were entirely refractory to the treatment, but the eosinophils were 6 and 8 per cent, respectively, this being the only evidence of the reaction.

Seven cases showed a low normal platelet count and normal coagulation time. The red cell count and hemoglobin were not particularly affected.

TABLE 1.—*Findings in Twenty-Four Patients with Chorea Treated with Phenylethyl-Hydantoin*

| Case | Age, Years | Sex | Severity | Duration of Chorea | White Blood Count | | Eosinophils | Tonsils | Temperature, F.* | Carbon Dioxide, Volumes per Cent† | Carditis | Results |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Before Rash | After Rash | | | | | | |
| 1 | 12 | F | 2 plus | 3 months | 10,600 | 6,900 | 4% | Removed | 103.0 | .. | None | Marked improvement within 22 days |
| 2 | 10 | F | 2 plus | 2 years | 8,400 | 7,600 lymphocytes, 61% polymorphonuclears, 24% | 5% | Removed | 103.4 | 56 | Present | Well within 24 days |
| 3 | 7 | F | 3 plus | 1 year, 1 year | 9,200 | 18,400 | 2% | Not removed | 106.0-107.0 | 58 | None | Died 9 days after admission |
| 4 | 9 | M | 2 plus | 2 attacks | 8,200 | 7,800 | 5% | Removed | 100.0 | .. | None | Well within 23 days; recurrence |
| 5 | 9 | M | 3 plus | 2 yrs., 4 mos. | 8,400 | 8,000 | 10% | Removed | 105.0 | .. | None | Well within 11 days |
| 6 | 7 | F | 2 plus | 3 months | 9,600 | 11,000 | 2% | Removed | 105.0 | .. | None | Well within 14 days |
| 7 | 11 | M | 3 plus | 5 months | No rash | | 6% | Not removed | 104.0 | 43 | None | Well within 14 days |
| 8 | 8 | F | 3 plus | 3 months | 9,600 | 9,700 | 12% | Removed | 103.0 | .. | Present | Well within 15 days |
| 9 | 6 | M | 3 plus | 2 months | 10,000 | 8,400 polymorphonuclears, 50% lymphocytes, 45% | 4% | Not removed | 103.0 | .. | Present | Well within 33 days |
| 10 | 9 | F | 3 plus | 8 months | 10,800 | 9,600, 5,200 | 5% | Removed | No fever | .. | None | Well within 24 days; red cell casts in urine; recurrence; no fever, no rash, but showed eosinophils |
| 11 | 9 | F | 3 plus | 16 days | No rash | ..... | 8% | Not removed | 102.0 | .. | None | Well within 38 days |
| 12 | 7 | F | 3 plus | 2 months | 7,900 | 7,000 | 7% | Removed | 102.0 | .. | None | Well within 37 days; encephalogram; nystagmus developed in both eyes |
| 13 | 12 | .. | 2 plus | No cure | 8,100 | 8,200 | 8% | Removed | No fever | .. | Present | No improvement (190 grains [12.3 Gm.] given within 50 days, with no toxic signs) |
| 14 | 10 | M | ..... | ..... | 7,200 | 10,200 | ... | Removed | 103.0 | 49 | Present | Well within 30 days; rash lasted 2 days; well within 17 days; rheumatism 4 months before; Wassermann reaction negative |
| 15 | 10 | M | ..... | ..... | ..... | ..... | 5% | Removed | 101.0 | .. | Present | Well within 18 days; recurrence; had received phenylethyl-hydantoin 3 months before; 10 treatments within 10 days |
| 16 | 14 | F | 2 plus | 10 days | 8,400 | 6,800 | 3% | ..... | ..... | .. | ..... | Well within 20 days; showed albumin in urine |
| 17 | 14 | F | 2 plus | ..... | 5,600 | 11,000 | 2% | Not removed | 104.0 | 52 | None | Well within 16 days |
| 18 | 4 | M | 3 plus | 2 weeks | 15,000 | 16,800 | 7% | Not removed | 105.0 | .. | Present | Well within 15 days |
| 19 | 7 | .. | 1 plus | 2 months | 9,000 | 7,200 | 1% | Not removed | 102.0 | .. | None | Well within 29 days |
| 20 | 7 | F | 1 plus | 23 days | 8,900 | 8,500 | 3% | Removed | 102.0 | .. | None | Well within 23 days |
| 21 | 8 | F | 1 plus | 8 months | 8,100 | 5,400 | 5% | Removed | 103.0 | .. | None | Well within 25 days |
| 22 | 11 | M | 2 plus | 3 months | 7,900 | 6,200 | 2% | Not removed | 103.5 | .. | None | Better within 20 days |
| 23 | 6 | F | 3 plus | 3 years | 8,100 | 8,900 | 1% | Not removed | 104.0 | .. | Present | Better within 24 days |
| 24 | 7 | M | 3 plus | 2 years | 9,000 | 8,500 | 6% | Not removed | 105.0 | .. | Present | Better within 31 days |
| Average duration..... | | | | | | | | | | | | 24½ days |

* In this table and the succeeding tables the temperature indicates the highest peak reached.
† Obtained by the Van Slyke method.

Analysis of the spinal fluid showed no change in any of the cases. The carbon dioxide volume per cent was studied in five cases at the height of the rash. I noted no appreciable changes to warrant placing the condition in the category of acidosis, as has been intimated by certain writers recently. The urinary findings were positive in three cases following the rash.

*Effect on Choreic Movements.*—The effect of phenylethyl-hydantoin on chorea in the cases studied was first an increase in choreic movements, which was most obvious during the reaction, and later a decrease, which was slow or rapid. There was relative drowsiness shortly before the appearance of the rash.

*Secondary Reactions.*—Patient 3 came to the hospital with severe chorea. She had been ill for one year. The heart sounds were not altered. She received 65 grains (4.2 Gm.) of phenylethyl-hydantoin and showed a morbilliform rash on the eighth day. The rash was pronounced and covered the entire body. On the first day following its appearance she became semicomatose; the temperature was 107 F., the pulse rate 225 and the respiratory rate 48. She showed cyanosis, labored breathing, a systolic bruit at the apex of the heart and obvious cardiac enlargement. The knee jerks were absent, and the whole body was flaccid. The urine showed 2 plus albumin and granular casts with a few red blood cells. Chemical examination of the blood revealed 20 mg. of urea nitrogen per hundred cubic centimeters. The blood sugar content was 76.9 mg. per hundred cubic centimeters, and the creatinine content was 1.9 mg. Examination of the spinal fluid gave essentially negative results. The blood count on admission was 8,600 white blood cells, with 60 per cent polymorphonuclears and 38 per cent lymphocytes. After the rash the blood count showed 18,400 white cells, with 62 per cent polymorphonuclears, 33 per cent lymphocytes and 4 per cent eosinophils. Intravenous injections of dextrose were given; ice-caps were applied for the high fever, and hydrotherapeutics was instituted, but the patient never regained consciousness. Two hours before she died she showed edema of the lungs.

In the series of patients treated with phenylethyl-hydantoin, from 5 to 10 grains (0.3 to 0.6 Gm.) of the drug was given orally in tablet form. Mautner[2] considered pyrexia essential to improvement in chorea. This was not verified in this series.

Two patients who were apparently refractory to the drug were afebrile but showed from 6 to 8 per cent eosinophils and were definitely improved within from twelve to fourteen days. In five patients of this series leukopenia developed.

### RESULTS OF TREATMENT WITH TYPHOID AND TYPHOID-PARATYPHOID VACCINE

Seven patients were treated with typhoid vaccine, and sixteen with typhoid-paratyphoid vaccine. The effects of the administration of these

2. Mautner, H.: Wien. klin. Wchnschr. **40**:627, 1927.

TABLE 2.—*Findings in Twenty-Three Patients with Chorea Treated with Typhoid-Paratyphoid Vaccine*

White Blood

Carbon Dioxide,

TABLE 2.—*Findings in Twenty-Three Patients with Chorea Treated with Typhoid-Paratyphoid Vaccine*

| Case | Age, Years | Sex | Severity | White Blood Count | | Calcium, Mg. | | Tonsils | Temperature, F. | Phosphorus | Carbon Dioxide, Vols. % | | Chlorides | | Carditis | Results |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Before Vaccine | After Vaccine | Before Fever | After Fever | | | | Before Vaccine | After Vaccine | Before Vaccine | After Vaccine | | |
| 1 | 7½ | M | 3 plus | 9,000 | 11,000 | 9.0 | 9.5 | Not removed | 104.5 | ... | 58 | 53.0 | 750 | 500 | None | Well within 10 days after 6 injections of typhoid-paratyphoid vaccine |
| 2 | 10 | F | 3 | 7,800 | 9,000 | .... | .... | Not removed | 104.0 | ... | .. | .... | ... | ... | None | Well within 10 days after 5 injections; had similar treatment 2 years before |
| 3 | 11 | F | 3 plus | ..... | ..... | 9.0 | 10.0 | Removed | 105.0 | 4.0 | 52 | 42.0 | 560<br>505 | 435<br>495 | None | Well within 29 days after 12 injections of from 15,000,000 to 1,750,000,000 Bacillus typhosus organisms; sinus infection |
| 4 | 11 | M | 3 | 9,000 | 9,200 | 11.0 | 12.6 | Not removed | 105.0 | ... | 60 | 34.0 | 520 | 430 | None | Well within 12 days; had chorea intermittently for 5 years; pulse rate dropped from 94 to 54 |
| 5 | 10 | F | 3 plus | 8,000 | 10,000 | 7.9 | 9.0 | Not removed | 104.5 | ... | 52 | 48.0 | 480<br>680 | 400<br>525 | None | Well within 17 days; 12 injections |
| 6 | 9 | M | 3 | 7,800 | 12,000 | 11.0 | 11.5 | Not removed | 105.5 | ... | 58 | 37.0 | 525 | 470 | Present | Well within 12 days; 10 injections |
| 7 | 11 | M | 3 plus | 9,000 | 12,000 | 8.2 | 9.7 | Removed | 103.0 | ... | 50<br>46 | 42.0<br>40.0 | 500 | 480 | None | Fifteen injections; somewhat refractory to treatment; not much improvement within 30 days |
| 8 | 10 | F | 3 plus | 8,000 | 10,000 | 9.2 | 10.5 | Removed | 104.5 | 3.9 | 46 | 40.0 | 520 | 410 | None | Fourteen injections within 31 days; had chorea for 2 years |
| 9 | 13 | F | 3 | 8,000 | 9,000 | .... | .... | Removed | 105.0 | ... | .. | .... | ... | ... | None | Well within 13 days; 5 injections; had 7 attacks each year for the previous 7 years |
| 10 | 14 | F | 3 plus | 7,200 | 9,500 | .... | .... | Removed | 105.6 | ... | .. | .... | ... | ... | None | Well within 8 days; 4 injections |
| 11 | 13 | F | 3 | 8,600 | 11,000 | .... | .... | Removed | 103.5 | ... | 44 | 23.0 | 495 | 480 | None | Two injections; had chorea 8 months before; well within 12 days |
| 12 | 12 | .. | 3 plus | 9,300 | 11,200 | 9.0 | 11.5 | Not removed | 104.5 | ... | 55<br>40<br>54 | 33.0<br>35.0<br>35.0 | 600<br>495 | 485<br>480 | Present | Well within 14 days; 8 injections |
| 13 | 8 | .. | 3 plus | 9,000 | 10,200 | 8.5 | 12.6 | ..... | 106.0 | ... | 46<br>51<br>58 | 38.0<br>33.0<br>53.0 | 530<br>520 | 490<br>495 | Present | Delirious onset, with chill; 9 injections; high blood calcium content; infection of frontal sinus; cure within 27 days |
| 14 | 7 | F | 3 | 10,000 | 9,500 | .... | .... | Not removed | 104.4 | ... | 56<br>50 | 50.0<br>45.0 | 560 | 440 | None | Well within 31 days |
| 15 | 8 | M | 3 plus | 8,500 | 9,500 | 9.5 | 13.5 | Removed | 106.8 | 5.0 before vaccine<br>4.3 after vaccine | 54 | 44.0 | 550<br>560 | 345<br>550 | None | Improvement within 5 days; 6 injections |
| 16 | 9 | F | 3 plus | 8,000 | 11,000 | .... | .... | ..... | 106.0 | 4.2 | 47<br>53 | 45.0<br>41.0 | 535 | 460 | Present | Well within 18 days; 12 injections; hemichorea |
| 17 | 8 | F | 3 plus | 7,800 | 10,100 | 11.8<br>11.5 | 12.2<br>13.0 | Removed | 105.0 | 4 to 5 | 60 | 57.8 | 550<br>510 | 540<br>510 | Present | Had 3 attacks previously at the ages of 6 and 7; 6 injections; well within 10 days |
| 18 | 7 | F | 3 plus | 15,000 | 17,000 | .... | .... | ..... | ..... | ... | .. | ..... | ..... | ... | ..... | Pneumonia; no treatment |
| 19 | 11 | M | 2 plus | 10,000 | 11,000 | 9.0 | 10.0 | Removed | 104.0 | 4.9 | 50 | 46.0 | 580 | 500 | None | Two attacks; well within 10 days; 8 injections |
| 20 | 6 | M | 3 | 9,200 | 12,500 | 9.2 | 11.0 | Not removed | 105.0 | 4.8 | 55 | 45.0 | 570 | 475 | None | Well within 12 days; 6 injections |
| 21 | 9 | F | 2 plus | 8,000 | 11,100 | 0.0 | 0.0 | Removed | 106.0 | ... | 60 | 40.0 | 595 | 485 | Present | Well within 13 days; 5 injections |
| 22 | 12 | F | 3 plus | 11,000 | 12,000 | 8.5 | 11.2 | Not removed | 104.5 | ... | 55 | 48.0 | 610 | 580 | Present | Well within 17 days |
| 23 | 6½ | F | 2 plus | 9,000 | 9,000 | 11 plus | 11 plus | Not removed | 105.6 | 4.3 | .. | .... | 520<br>525 | 530 | None | Well within 6 days |

Average time required for cure..... 16⅝ days

vaccines were in some instances spectacular. In three cases the duration of the disease was about from thirty-one to thirty-two days. The average duration was approximately sixteen and two-thirds days or less. These figures are higher than those of Dr. Lucy Porter Sutton, who reported that in the twenty-four patients in her series who were treated with typhoid-paratyphoid vaccine the duration of the chorea from the day of treatment was seven and seven-tenths days in mild cases, seven and eight-tenths days in moderate cases and fourteen days in severe cases.

*Procedure.*—Typhoid-paratyphoid vaccine furnished by the New York City Health Department was given intravenously. It contained 1,000,000,000 typhoid bacilli and 750,000,000 paratyphoid bacilli per cubic centimeter. The initial dose was usually 50,000,000 organisms (or 0.05 cc.). This produced a sharp febrile reaction. Succeeding doses were determined according to the reaction produced by the first injection. If the reaction was sharp, the first dose was repeated.

TABLE 3.—*Reactions in Case 15 During a Course of Six Injections of Vaccine*

| | | | Blood Findings | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Blood Pressure | | Chlorides, Mg. | | Carbon Dioxide, Vols. % | | Calcium, Mg. | | |
| Day of Injection | Amount, Cc. | Temperature, F. | Before Vaccine | After Vaccine | Before Vaccine | After Vaccine | Before Vaccine | After Vaccine | Before Vaccine | After Vaccine | Phosphorus, Mg. |
| 1 | 50 | 105.4 | 90/30 | 90/40 | 550 | 345 | .. | .. | ... | ... | ... |
| 2 | 50 | 106.8 | 110/50 | 84/40 | ... | ... | .. | .. | ... | ... | ... |
| 3 | 50 | 105.6 | 96/62 | 98/20 | ... | ... | .. | .. | ... | ... | ... |
| 6 | 50 | 104.2 | 100/66 | 80/10 | 560 | 550 | .. | .. | ... | ... | 4.3 |
| 8 | 75 | 104.4 | ..... | ..... | ... | ... | .. | .. | ... | ... | ... |
| 12 | 75 | 105.2 | 96/88 | 88/25 | ... | ... | 54 | 44 | 9.5 | 12.6 | ... |

However, the dose was usually increased. The blood pressure was taken, and analysis of the blood was made before the injections and after the maximum rise in temperature. The patient was wrapped in several blankets soon after the injection and allowed to remain thus until the temperature fell. This usually took four or five hours. The temperature was taken every half hour. The chill was noted usually from one-half to one and one-half hours after injection. The reaction was more severe and sometimes the discomfort was noted to a greater degree if the patient had eaten before receiving treatment. It was also observed that the reaction was more severe and the temperature higher if the mixed vaccine was used rather than the typhoid vaccine. After the treatment was instituted the vaccine was given daily for the first three days, then every other day and finally every third day. The minimum number of injections given was usually six; and the maximum, fourteen. If the temperature was below 102 F., the dose was doubled on the following day. The doses were increased according to the severity of the reaction.

The data for case 15 may serve as an example of those for the entire series.

*Fever.*—The average rise in temperature for the twenty-three cases was to 105 F. Seven patients reacted with a rise in temperature to

106 F. plus. The chill occurred from one-half to one and one-half hours after the injection, and obvious discomfort was noted. In case 4 the pulse rate dropped from 94 to 54 on the first day and to 48 on the second day. Evidence of extrasystole was also noted. Within ten days the bradycardia disappeared. In five cases there were nausea and vomiting. The fever rose to its maximum within from one to one and a half hours after injection and lasted from three to five hours.

*Carbon Dioxide of the Blood.*—The carbon dioxide volume per cent of the blood was determined before and after the fever. This was sometimes estimated three or four times in each patient. In each instance the level of the carbon dioxide curve was lower after treatment than before. In case 11 of this series the curve was 23 volumes per cent. This was checked twice. It was noted that the higher the febrile reaction and the greater the amount of sweating, the lower the carbon dioxide curve.

*Chlorides.*—The chlorides showed a decline, particularly in patients who had been treated for four or five days and had shown a severe reaction. This is very likely due to the fact that during sustained fevers a considerable amount of sodium chloride is withdrawn from the blood and tissues as a result of sweating. The blood chloride determinations were made on whole blood. It was found that the higher the pyrexia and the greater the amount of sweating, the lower the chlorides.

*Calcium.*—The calcium content generally ranged from low normal to moderately low before the induction of fever. In one case, after eight injections of typhoid-paratyphoid vaccine the calcium level rose to 12.2 mg. per hundred cubic centimeters of blood. This was checked by different laboratories.

*Phosphorus.*—The phosphorus level was invariably slightly lower after four or five treatments.

*Spinal Fluid.*—Examination of the spinal fluid gave negative results for all the patients of the series. In one case, signs were referable to the central nervous system. An encephalogram was taken, but this gave negative findings.

*Blood Chemistry.*—No alteration was noted in the urea nitrogen. There was a moderate increase in the nonprotein nitrogen after injection, as compared with that of normal persons. The sugar also showed a slight increase in eight patients in which it was determined.

*Colloidal Gold.*—Colloidal gold tests on eleven patients revealed no typical curve for chorea.

*Blood Pressure.*—The blood pressure exhibited a moderate decline during the febrile period. The fall in the diastolic pressure was disproportionately greater than that in the systolic pressure.

*Hydrogen Ion Concentration.*—In only three patients was the $p_H$ of the blood determined. The concentrations were 7.4, 7.45 and 7.6. There was a moderate rise in all three.

### CHOREA WITH PNEUMONIA

A patient was admitted to the hospital with marked chorea. She had nasopharyngitis on admission, which developed into pneumonia on the following day. On the third day after admission the temperature rose to 105 F., remaining at that level for six days. The chorea became much improved within nine days. She was free from nervous symptoms within fourteen days. One speculates as to whether this improvement following pneumonia was due to the chemical changes produced during the febrile period.

Darrow and Hartmann,[3] in summarizing the chemical changes in eight cases of pneumonia, concluded:

> There is a lowering of the concentration of chloride and bicarbonate, and since there is no compensatory increase in the nonelectrolyte, there is a decrease in the osmolar concentration. . . . The carbon dioxide absorption curve is low in pneumonia, and the lower level is due to (1) the temperature effect and (2) lower concentration of base.

### FOLLOW-UP CASES

Seventeen patients who had received phenylethyl-hydantoin were seen later. Eleven had had one or more recurrences. Carditis had developed in six. Twelve patients who had received typhoid-paratyphoid vaccine were followed. No recurrences were observed in all these patients, and there was no evidence of carditis. The patients of the typhoid-paratyphoid series were treated for sixteen months, while those given phenylethyl-hydantoin were treated for three years.

### COMMENT

An analysis of the series treated with phenylethyl-hydantoin and typhoid-paratyphoid vaccine revealed that there were spectacular benefits from phenylethyl-hydantoin in some cases, but in the majority of cases the average duration of the disease was twenty-four days. In eight cases the condition was unimproved. In one case the drug caused a fatality. One is justified, therefore, in characterizing this method as of questionable value in the treatment of chorea.

The results of treatment with typhoid-paratyphoid vaccine showed that this form of therapy is not dangerous, but it produces obvious discomfort—chills and fever—during the febrile period. However, the duration of treatment with this preparation was shorter by eight days than that with phenylethyl-hydantoin, the average duration being about

3. Darrow, Dan, and Hartmann, Alexis: Chemical Changes Occurring in the Body as a Result of Certain Diseases, Am. J. Dis. Child. **37**:323 (Feb.) 1921.

sixteen days. There were no recurrences of chorea in patients treated with typhoid-paratyphoid vaccine who were followed for one year, and it was noted that carditis, the most dangerous sequel of chorea, did not occur in those treated with this preparation during this period. It is, of course, too soon to make any sweeping conclusions as to the advantages of treatment with typhoid-paratyphoid vaccine. However, I believe that this ought to be the treatment of choice. In my series of cases the time required to arrest the symptoms of chorea was from two to three days longer than in the patients treated by Dr. Sutton.

Speculating as to the factor responsible for the improvement in these cases, one is impressed by the chemical changes taking place during the febrile period when typhoid-paratyphoid vaccine is introduced. I noted a definite change in the acid-base equilibrium. There was invariably a low carbon dioxide content of the blood during the prolonged fever, with a low level for chlorides, a moderate raising of the calcium level and a lowering of the phosphorus level. It was noted in three cases that the $p_H$ of the blood was slightly increased coincidentally with the lowering of the carbon dioxide content. Is this sudden shift in the acid-base equilibrium operative in the improvement, or is improvement due to the increase in calcium during the febrile period? Although there is a lowering of the carbon dioxide volume per cent and the chloride level, there is an increase in $p_H$. The bases are not lost, but are bound to the proteins, owing to the increase in $p_H$. There is probably a sudden shift to alkalinity. I quote Bischoff, Ullmann, Hill and Long [4] on hyperthermia to confirm this hypothesis:

> Of all the changes taking place in the chemistry of the body following a gradual moderate rise in body temperature (37.0-39.4°) the one of fundamental importance is the loss of $CO_2$. This has been pointed out before by others. Our data illustrate this point very strikingly. The one effect which was the same in all the experiments was the rise in the blood $p_H$. This, in connection with the other data, showed conclusively a lowered $CO_2$ tension of the blood. The other changes, which in some instances did not follow, were a result of the lowering of the $CO_2$ tension. Thus, the $p_H$ of the urine remained unchanged or became more alkaline, the alkali reserve remained the same or increased, the inorganic phosphorus was unchanged or decreased, the calcium was unchanged or increased, the hemoglobin was more or less highly oxygenated. The change in the total $CO_2$ content of the blood is readily accounted for by the shift of base to the blood proteins due to the increase in $p_H$. Since the alkali reserve of the blood remains the same or increases slightly, and since the $p_H$ of the urine as excreted is not more alkaline than the blood, there is little reason for believing that the body is attempting to compensate for the lowered $CO_2$ tension by lowering the alkali reserve.

Diminution of the blood pressure was also noted during the febrile period. The pulse pressure fell disproportionately more than the systolic pressure.

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4. Bischoff, Fritz; Ullmann, H. J.; Hill, Elsie, and Long, M. L.: J. Biol. Chem. **85**:675, 1930.

Seventeen patients of the entire series treated with phenylethyl-hydantoin and typhoid-paratyphoid vaccine showed evidence of carditis on admission. Twenty-three patients of the entire series had had their tonsils removed. Eight showed roentgenographic evidence of sinus and antral involvement. All the patients treated with typhoid-paratyphoid vaccine gave a positive Widal reaction in all dilutions during their stay in the hospital.

## CONCLUSIONS

From these observations it is concluded that typhoid-paratyphoid vaccine proved of greater value in the treatment of chorea than phenyl-ethyl-hydantoin for the following reasons: (1) harmlessness, (2) shorter time required for cure, (3) probable arrest of recurrences, (4) ease of administration, (5) significant lack of sequelae and (6) the occurrence of chemical changes during the febrile period.

# BACTERIAL FLORA OF FIRST SPECIMENS OF MECONIUM PASSED BY FIFTY NEW-BORN INFANTS

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The main facts concerning the acquisition and character of the bacteria which are harbored in the human intestinal tract have been established and are documented in the work of Woodward,[1] Escherich,[2] Schild,[3] Szego,[4] Tissier,[5] Herter[6] Mannaberg,[7] Logan,[8] Kendall,[9] Rettger and Cheplin,[10] van der Reis[11] and others.

We know that the meconium is generally sterile at birth, that various bacteria appear in it within the first twenty-four hours of life,

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1. Woodward, J. J.: The Medical and Surgical History of the War of the Rebellion, Washington, D. C., Government Printing Office, 1879, pt. 2, p. 869.

2. Escherich, T.: Die Darmbakterien des Säuglings und des Neugeborenen, Fortschr. d. Med. **3**:515, 1885; Ueber Darmbakterien im Allgemeinen und diejenigen der Säuglings im Besonderen, sowie die Beziehungen der letzteren zur Aetiologie der Darmerkrankungen, Centralbl. f. Bakt. **1**:705, 1887.

3. Schild, W.: Das Auftreten von Bakterien im Darminhalte Neugeborener vor der ersten Nahrungsaufnahme, Ztschr. f. Hyg. **19**:113, 1895.

4. Szego, K.: Die Darmmikroben des Säuglings und der Kinder, Arch. f. Kinderh. **22**:25, 1897.

5. Tissier, H.: Recherches sur la flore intestinale des nourrissons (état normal et pathologique), Thèse de Paris, 1900.

6. Herter, C. A.: The Common Bacterial Infections of the Digestive Tract, New York, The Macmillan Company, 1907.

7. Mannaberg, J.: The Bacteria of the Intestine, in Nothnagel, C. W. H.: Encyclopedia of Practical Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1907, p. 38.

8. Logan, W. R.: Intestinal Flora of Infants and Chlidren, J. Path. & Bact. **18**:527, 1914.

9. Kendall, A. I.: Recent Developments in Intestinal Bacteriology, Am. J. M. Sc. **156**:157, 1918.

10. Rettger, L. T., and Cheplin, H. A.: The Transformation of the Intestinal Flora with Special Reference to the Implantation of Bacillus Acidophilus, New Haven, Conn., Yale University Press, 1921.

11. van der Reis, V.: Die Darmbakterien des Erwachsenen und ihre klinische Bedeutung, Ergebn. d. inn. Med. u. Kinderh. **27**:77, 1925.

that the flora of the first three or four days is complex, that simplification accompanies the establishment of normal lactation and nursing and the appearance of the characteristic milk stool, and continues as long as the nursing baby is in good health, that diversification in the flora accompanies intestinal disturbances during the nursing period and normally follows weaning and the substitution of a more varied diet, and that even in the adult a preponderance of lactose, in milk or otherwise, or of dextrin in the diet may again bring about a simplification of the intestinal flora in the direction of that shown by a healthy nursing infant.

Microscopic examination of the feces reveals much that can be interpreted clinically, but exact knowledge requires meticulous cultural studies, both aerobic and anaerobic, with isolation and careful identification of pure cultures. After the first few days of life obligately anaerobic bacteria generally outnumber the aerobes, as Eggerth and Gagnon [12] clearly showed, and unless highly specialized procedures are adopted for their detection the lack of correlation between microscopic and cultural examination is likely to be most perplexing. The quantitative and qualitative complexity of the intestinal flora is often such that no combination of methods now known gives true intestinal analysis. The bacteriologist merely determines the presence of certain predominating micro-organisms the varied metabolic requirements of which happen to be met by the culture mediums used and the particular environmental conditions provided. We believe that there is still much to be learned concerning the ebb and flow of the intestinal flora and the taxonomic relationships and properties of the various species of bacteria involved.

Our decision to reinvestigate the bacteriology of first specimens of meconium was determined by: (1) a curiosity as to the possible presence in meconium of sporulating bacilli, either aerobic or anaerobic, particularly of Bacillus tertius, which one of us (I. C. H.) with Matsumura,[13] in 1924, found in four of eight specimens of feces from Japanese nurslings; (2) the observation of Burrage,[14] in 1927, that only 62 per cent of the specimens of meconium first passed by nearly one hundred infants were sterile, and (3) the availability of improved anaerobic technics.[15]

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12. Eggerth, A. H., and Gagnon, B. H.: The Bacterioides of Human Feces, J. Bact. **25**:389, 1933.

13. Hall, I. C., and Matsumura, K.: Recovery of Bacillus Tertius from Stools of Infants, J. Infect. Dis. **35**:502, 1924.

14. Burrage, S.: Bacteria in the Supposedly Sterile Meconium, J. Bact. **13**:47, 1927.

15. Hall, I. C.: The Study of Obligately Anaerobic Bacteria, Society of American Bacteriologists, Manual of Methods for Pure Culture Study of Bacteria, ed. 2, 1932, Leaflet 3.

## METHODS

Sterile diapers were used in the maternity ward, and the nurses were instructed to bring to the laboratory as soon as possible each first specimen of meconium passed, wrapped in the diaper together with the baby's name, hospital number and time that the specimen was collected. The baby's sex, time of birth, weight at birth and periods elapsing after placental rupture were obtained later from the histories; the color, consistency, odor and amount of the specimen were noted on delivery to the laboratory.

A large loop of each specimen was first suspended in sterile water sufficient to produce marked turbidity. A colorimetric determination of $p_H$ was then made, and two slides were prepared for microscopic examination, one stained with Löffler's methylene blue and one by Gram's method.

A cultural examination was made for aerobes by streaking the primary suspensions on eosin methylene blue lactose agar plates and blood agar plates and for obligate anaerobes in dextrose broth constricted tubes and deep iron brain medium, following the technics described by one of us (I. C. H.).[15] Every possible micro-organism was isolated in pure culture and carefully identified by approved methods. A Findex analyzer[16] was used in tabulating the data.

## OBSERVATIONS

*Microscopic.*—No bacteria could be recognized by either methylene blue or Gram's stain in forty-seven specimens. Three specimens showed gram-positive cocci (Micrococcus candidus); one of the three also showed gram-negative rods (Bacterium coli) and another, large gram-positive rods (Bacillus Welchii). The three specimens which were microscopically positive came from babies 13, 26 and 17 hours old. No bacteria resembling Lactobacillus bifidus or Lactobacillus acidophilus were seen in any of the first specimens. Forty-five of the specimens came from babies less than 15 hours old, and only one showed micro-organisms in sufficient numbers to be detected microscopically. It is clear that as a rule microscopic examination of first specimens of meconium yields no positive information of value.

*Cultural.*—The cultural data are summarized in tables 1, 2 and 3.

Of the fifty specimens, thirty-one proved sterile in all of the inoculated mediums, while nineteen contained bacteria. It may be significant as bearing on a possible criticism of our plan of securing specimens on sterile diapers instead of using the more approved methods of anal cannulation, that in all but four instances, when bacteria were recovered from any of the cultures from a specimen, the colonies were so numerous on the eosin methylene blue and blood agar plates as to leave no doubt regarding their actual presence in relatively large numbers in the specimen itself. There were only four specimens in which the bacteria found might be interpreted as being present in such small numbers as to require enrichment for their demonstration. The

16. Made by the Findex Company, 49 East Wells St., Milwaukee.

organisms recovered in these enriched cultures but not found on plates streaked directly from fresh suspensions were Micrococcus epidermidis, Micrococcus albus and Micrococcus ureae.

It seems unlikely also that the organism found in such large numbers in fifteen specimens can be interpreted to represent contaminations from the exterior. In any event the actual percentage of total positive results closely approximates those of Burrage,[14] who used the same method of collection.

Micrococci were found in fifteen specimens and were represented by four species, all white: M. albus, M. candidus, M. epidermidis and M. ureae, according to Hucker's classification. It is interesting to note that no streptococci were encountered, in spite of Dudgeon and Jewesbury's

TABLE 1.—*Relation of Bacterial Observations on Fifty First Specimens of Meconium to Period Elapsing Between Rupture of the Placental Membrane and Birth*

| Bacterial Observations | Total Number of Specimens | Hours | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1 or Less | 1 to 5 | 5 to 10 | 10 to 20 | 20 to 30 | 30 to 40 | No Record |
| Sterile | 31 | 11 | 5 | 4 | 1 | 1 | 0 | 9 |
| Micrococcus (albus, candidus, epidermidis, ureae) | 15 | 4 | 2 | 0 | 1 | 1 | 1 | 6 |
| Bacterium (coli, aerogenes, paratyphosum B) | 6 | 3 | 0 | 1 | 0 | 0 | 1 | 1 |
| Bacillus Welchii | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total number of specimens | 50 | 18 | 7 | 5 | 2 | 2 | 1 | 15 |
| Percentage of sterile specimens | 62 | 61 | 71 | 80 | 50 | 50 | 0 | 60 |

demonstration of streptococci in forty-nine of one hundred samples of human milk.[17]

Bact. coli was represented in six specimens, Bacterium aerogenes in one and Bacterium paratyphosum B (!) in one, the last two being separately associated with Bact. coli.

The finding of Bact. paratyphosum B in a first specimen of meconium was so unusual that we were led into considerable speculation as to its origin and its significance. The baby was a normal girl, weighing 5 pounds and 4 ounces (2.381 Gm.). There was no record of the time at which placental rupture occurred in the mother. The first specimen of meconium passed measured only 5 cc., was black and mucoid and was secured twenty-six hours after birth. It had a $p_H$ of 6.2, and contained in addition to Bact. paratyphosum B, Bact. coli and M. candidus. Reexamination of the feces on the ninth day for aerobes again gave the same findings. The baby showed no unfavorable

17. Dudgeon, L. S., and Jewesbury, R. C.: The Bacteriology of Human Milk, J. Hyg. **23**:64, 1924.

symptoms and was presumably immune. The mother was likewise well and the presence of Bact. paratyphosum could not be demonstrated in a single examination of her normal feces. Her blood serum likewise failed to agglutinate the culture of Bact. paratyphosum B recovered from the baby's stools in serum dilutions of 1:20, 1:200 and 1:2,000.

B. Welchii was found once, in the scanty, black, mucoid meconium passed by an 8 pound (3,628 Gm.) girl, 17 hours old, born within an hour of the placental rupture. B. Welchii was associated with Bact. aerogenes and Bact. coli. The fact that large gram-positive rods resembling B. Welchii were seen in the direct microscopic examination of this specimen practically precludes the possibility of accidental con-

TABLE 2.—*Relation of Bacterial Observations on Fifty First Specimens of Meconium to Sex, Weight and Age of Infants*

| Bacterial Observations | Total No. of Specimens | Sex | | Approximate Weight in Pounds | | | | | Ages in Hours | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Male | Female | 4 Pounds | 5 Pounds | 6 Pounds | 7 Pounds | 8 Pounds | 0 to 5 | 5 to 10 | 10 to 15 | 15 to 20 | 20 to 25 | 25 to 30 |
| Sterile | 31 | 16 | 15 | 3 | 3 | 14 | 6 | 5 | 7 | 18 | 5 | 1 | 0 | 0 |
| Micrococcus (albus, candidus, epidermidis, ureae) | 15 | 10 | 5 | 0 | 1 | 2 | 9 | 3 | 1 | 5 | 6 | 2 | 0 | 1 |
| Bacterium (coli, aerogenes, paratyphosum B) | 6 | 0 | 6 | 0 | 3 | 2 | 0 | 1 | 0 | 2 | 2 | 1 | 0 | 1 |
| Bacillus Welchii | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Total number of specimens | 50 | 26 | 24 | 3 | 6 | 17 | 15 | 9 | 8 | 25 | 12 | 4 | 0 | 1 |
| Percentage of sterile specimens | 62 | 61 | 62 | 100 | 50 | 82 | 40 | 55 | 87 | 72 | 41 | 25 | 0 | 0 |

tamination. No other sporulating bacilli were isolated in the entire series.

## THE RELATION OF VARIOUS FACTORS TO THE STERILITY OF MECONIUM

*Period from Placental Rupture to Birth.*—The time of placental rupture was recorded in thirty-five cases. Of these, twenty-two specimens (63 per cent) were sterile, while nine (60 per cent) of fifteen unrecorded specimens were sterile. In thirty instances placental rupture was followed by birth within ten hours; twenty (66⅔ per cent) of these resulted in sterile meconiums. In five instances placental rupture was followed by birth in from ten to thirty-nine hours; only two (40 per cent) of these resulted in sterile meconium, but the number of delayed births is obviously too small to justify conclusions. No definite relation between the placental rupture and the sterility of the first specimen of meconium was proved.

*Sex.*—Twenty-six of the specimens came from male and twenty-four from female babies. Of the former, sixteen specimens (61 per cent) were sterile; of the latter, fifteen (62 per cent). Thus, there was no correlation with sex.

*Weight and Age.*—Although the percentage of sterile specimens from babies of different weights varied greatly, it is impossible to consider that there was any regular correlation. Sixteen per cent of the babies passed the first specimen of meconium before they were 5 hours old, 50 per cent between the fifth and the tenth hour, 8 per cent between the fifteenth and twentieth hour and 2 per cent as late as the twenty-sixth hour. Since it is customary in our hospital to put the babies to the breast about ten hours after birth, thirty-three of the specimens

TABLE 3.—*Relation of Bacterial Observations in Fifty First Specimens of Meconium to Amount of Specimen, Color, Consistency and* $p_H$

| Bacterial Observations | Total No. of Specimens | Amount in Cubic Centimeters | | | | Color | | | Consistency | | $p_H$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 15 | 20 | Black | Green | Brown | Mucoid | Dry | 6 | 6.2 | 6.4 | 6.6 |
| Sterile | 31 | 7 | 16 | 4 | 4 | 18 | 5 | 8 | 26 | 5 | 6 | 16 | 7 | 2 |
| Micrococcus (albus, candidus, epidermidis, ureae) | 15 | 5 | 6 | 4 | 0 | 11 | 2 | 2 | 9 | 6 | 5 | 8 | 2 | 0 |
| Bacterium (coli, aerogenes, paratyphosum B) | 6 | 2 | 4 | 0 | 0 | 5 | 1 | 0 | 5 | 1 | 1 | 3 | 2 | 0 |
| Bacillus Welchii | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| Total number of specimens | 50 | 13 | 25 | 8 | 4 | 32 | 8 | 10 | 38 | 12 | 11 | 26 | 11 | 2 |
| Percentage of sterile specimens | 62 | 54 | 64 | 53 | 100 | 56 | 62 | 80 | 68 | 42 | 55 | 61 | 64 | 100 |

were secured before feeding began. Twenty-five (76 per cent) specimens were sterile, but perhaps the corollary is more interesting; 24 per cent contained bacteria.

As would be expected, age seemed to be the most striking factor in the sterility of the first meconium passed, because there was a gradually decreasing percentage of sterile specimens from five to twenty hours after birth. No sterile specimens were secured after twenty hours; but since only one specimen was passed that late it is perhaps only a coincidence that it contained Bact. paratyphosum B.

*Amount of Specimens.*—Twenty-five of the fifty specimens were approximately 10 cc.; 64 per cent of these were sterile. All four of the specimens measuring 20 cc. were sterile, but the fact is probably not significant. There was no correlation between the amount of the specimens and the age of the baby.

*Color of Specimens.*—Thirty-two specimens were nearly black, eight were green and ten were brown. Eighty per cent of the brown specimens were sterile.

*Consistency.*—Thirty-eight specimens were received in a moist condition; twelve were nearly dry. The percentage (68) of sterile specimens among the former was above the average of 62 for the series; that of the latter (42) was distinctly below.

All of the dry specimens were small in amount, i. e., less than 10 cc., and 75 per cent of them were less than 5 cc.

*Hydrogen Ion Concentration.*—The $p_H$ values ranged from 6 to 6.6, with the mode at 6.2 given by twenty-six of the total number tested; eleven gave a value of 6, eleven 6.4 and only two 6.6. Although both the last two were sterile their number is too small to regard as significant, and the percentage of sterile samples in the other acidities closely approximated that for the whole series.

At the time our data were obtained we were not familiar with the technic of dialysis proposed by Tisdall and Brown [18] and used by Norton and Shohl,[19] who found an average $p_H$ of 6.08 for fourteen specimens of meconium passed the first day, with a range from 5.7 to 6.3. The results of Norton and Shohl are interesting in showing the progressive increase in acidity to a $p_H$ of 4.88 on the tenth day.

## CONCLUSIONS

1. About 94 per cent of the first specimens of meconium passed by infants fail to show bacteria on microscopic examination.

2. Bacteria may be demonstrated microscopically occasionally (6 per cent) in first specimens of meconium passed twelve hours after birth.

3. About 38 per cent of the first specimens of meconium may be demonstrated culturally to contain aerobic bacteria. Although only 13 per cent of the specimens passed during the first five hours contain bacteria, the percentage rises rapidly to 100 per cent during the first twenty-four hours of life.

4. The predominating bacteria are white micrococci and Bact. coli; sporulating bacilli and streptococci are rare.

5. Bact. paratyphosum B and B. Welchii were found once in fifty first specimens.

6. No relation between the rupture of the placental membranes and the presence or absence of bacteria in first specimens has been proved.

7. The hydrogen ion concentration of first specimens of meconium varies between $10^{-6}$ and $10^{-6.6}$.

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18. Tisdall, F. F., and Brown, A.: Studies on the Acidity (Hydrogen Ion Concentration) of Infants' Stools, Am. J. Dis. Child. **27**:312 (April) 1924.

19. Norton, R. C., and Shohl, A. T.: Hydrogen Ion Concentration of the Stools of New-Born Infants, Am. J. Dis. Child. **32**:183 (Aug.) 1926.

# SO-CALLED BREAST MILK INTOXICATION

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There are many cases of infantile beriberi (kakke) in Japan. In most instances the mother of the afflicted infant has beriberi. However, sometimes the mother is healthy (concealed beriberi). Ito observed such a case in which the mother did not have beriberi and called the condition "mother's milk intoxication." But he afterward changed this name to "breast milk intoxication" because he saw cases in babies who were nourished with the milk of wetnurses.

After many heated discussions at their annual meetings most of the Japanese pediatricians came to believe in the existence of concealed beriberi. There is no means of recognizing concealed beriberi, however, except by experiments on infants. So it was decided to allow the name "breast milk intoxication" with a prefix "so-called."

So-called breast milk intoxication is seen only in breast-fed infants. If the baby discontinues the breast milk that is causing the disturbance and takes another food (such as cow's milk, condensed milk or the milk of a healthy nurse), it recovers in a short time. Therefore, the milk of the mother or nurse must contain something that causes the infant to become sick or must lack some food property necessary for proper growth.

In 1913, Segawa reported an interesting case in which nervous symptoms in a breast-fed infant disappeared when mixed feedings were given. The mother of the patient did not have beriberi; so Segawa was of the opinion that in addition to infantile beriberi there is another disease of infants due to breast feeding. This was the first case reported of what is now termed so-called breast milk intoxication. The nervous symptoms vanished quickly when the mother ceased to nourish the baby with her breast milk and reappeared when the milk of the mother was again used. Segawa concluded, therefore, that the cause of the sickness must lie in the breast milk but that the malady is not the same as infantile beriberi. In time the name so-called breast milk intoxication was used only in cases like that of Segawa.

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The clinical part of this study was done mainly in the section of pediatrics (Prof. S. Ito, director) of the Kyushu Imperial University. The histologic studies were made in the Kwangtung Government Hospital in Port Arthur.

Karasawa examined sections from a case of so-called breast milk intoxication for the first time in 1917, but he was unable to find pathologic changes in the brain.

In the same year Inaba insisted that although cardiac disturbances are the important symptoms of infantile beriberi, the nervous manifestations which are the characteristic symptoms of so-called breast milk intoxication may also be seen in infantile beriberi and are not incompatible with that diagnosis. He referred to Ikeda's case, which showed distinct alteration of the cerebrospinal fluid. He expressed the belief that the paralytic signs of so-called breast milk intoxication may be peripheral.

In 1918 Karasawa reported pathologic observations in two cases of so-called breast milk intoxication. In the first case the important gross changes were fatty degeneration and brown pigmentation of the heart, liver and kidneys and hyperemia of the leptomeninges; sections stained with hematoxylin and eosin showed slight microscopic hemorrhages around the blood vessels, cellular infiltration of the leptomeninges, slighter cellular infiltration of the brain and general fatty degeneration of the liver. In the second case he noted hyperemia of the leptomeninges, central fatty degeneration of the liver and catarrhal irritation of the stomach and intestines.

Because of the rapidity of recovery from so-called breast milk intoxication when the patients are given vitamin B, Toyoda thought that the cause of this sickness was the same as that of infantile beriberi.

In 1922 I observed a typical case of so-called breast milk intoxication and concluded that the condition must be pontile encephalitis because the patient had cross-paralysis and other general symptoms of involvement of the brain. Afterward I observed many cases and found instances of this disease in association with polioencephalitis haemorrhagica superior (and inferior) acuta (C. Wernicke) on the basis of clinical observation. Unfortunately I had no chance to examine sections for some time, since the disease is seldom fatal. However, in 1929 I had a case, to be reported in this paper in which the patient died after a few days' illness. The parent allowed me to dissect only the brain, which I examined carefully, especially the pons, medulla oblongata and lamina quadrigemina, which I cut serially. The results of examination verified my clinical diagnosis.

## ETIOLOGY

There are two opinions as to the etiology of so-called breast milk intoxication: (1) that the cause is the same as that of infantile beriberi, the condition being a new, cerebral type of infantile beriberi, and (2)

that there is an unknown, independent cause, the condition being a new, independent disease. According to both theories, however, the breast milk which the baby takes is responsible for the illness.

It is interesting that in most instances infantile beriberi is found in babies about 2 months old whereas so-called breast milk intoxication usually occurs at the age of dentition (about 7 months).

The following tabulation will show this relation:

| Age, Months | No. of Cases |
|---|---|
| 2 | 1 |
| 5 | 2 |
| 6 | 3 |
| 7 | 6 |
| 8 | 4 |
| 9 | 5 |
| 10 | 3 |
| 11 | 4 |
| 13 | 2 |
| 14 | 1 |
| Total | 31 |

Reports of cases have come from every part of Japan (Japan proper, Shikoku, Kyushu, Hokushu, Chosen and Formosa) and from Kwangtung and Manchuria, where Japanese live.

### SYMPTOMATOLOGY

The first manifestations are dyspeptic symptoms, such as green diarrhea and vomiting, which occur before the characteristic nervous signs appear. So it is difficult in the beginning to distinguish between simple dyspepsia and this malady. The baby becomes irritable and pale. Seldom do the cerebral symptoms attack the child without prodromal dyspeptic signs. The dyspeptic period is of variable duration, sometimes a few days and sometimes more than a month. Following the dyspeptic stage general cerebral symptoms appear, such as irritability or dulness, uneasiness, poor concentration, disturbed sleep and sometimes sopor. Disorders of consciousness are always seen, but they are not so distinct before convulsions take place, so that even the mother does not notice them. The expression of the face and eyes becomes dull. Motion of the eyes is slow and infrequent, and ptosis is almost constantly seen. The baby forgets to cry and to smile, but abnormal laughing, such as menacing laugh, often occurs. If lactation has ceased, all these symptoms quickly disappear, but if not, the baby shows further manifestations, such as abnormal position of the eyeballs, sopor, flopping of the upper or lower limbs, choreic athetotic motions of the arms or motions like those made in washing the face or in searching for some-

thing about the pillow. Nystagmus of various types also appears. Finally the patient is seized with convulsions, which usually involve the whole body. After the convulsions consciousness becomes more or less obscured and many sorts of paralysis appear, such as cross-paralysis of several parts, monoplegia of nerves of the brain or hemiplegia.

Disturbance of static tonicity is the most important and constant symptom, being present in all cases from the onset to the termination of the sickness, with decrease of muscle tonus of the whole body and ataxia. The patient cannot sit, crawl or even hold up the head.

In most cases the patellar tendon reflex is weakened, but frequently this reflex suddenly becomes strong again. Voluntary movement becomes unskilful, the patient's condition being reduced to that of a new-born infant; for example, he cannot hold up the head or grasp toys or a person at will. Local convulsions or tremors often occur. There are frequently characteristic movements expressive of irritation, such as flopping the limbs or rotating the body around the neck, with strong opisthotonos sustaining the whole body at the neck and the heels. These symptoms are not so characteristic as many authors state; they are not observed as frequently as disturbance of static tonicity, decrease of muscle tonus and ataxia and do not always occur even in advanced cases. Disturbance of sight is present in many cases, as well as axial optic neuritis.

Of the many symptoms which have been mentioned, paralysis of the outer muscles of the eyes, disturbance of static tonicity, expression and consciousness and decrease of muscle tonus (in the beginning) are the most important. And in all cases the disturbance of static tonicity is the last symptom to disappear.

## REPORT OF A CASE

*History.*—Y. T., a boy, aged 5½ months, was admitted to the Kwangtung Government Hospital in Port Arthur with chief complaints of weakness and sweating.

The baby was the first son of a mother who had suffered from nephritis for one month and was not yet well. She was pale but had no signs of beriberi. The baby was nourished with mother's milk only. Dentition and walking had not begun. The child had been vaccinated. The mental and physical development were almost normal.

The past history had no bearing on the present illness.

On the day before admission the baby became weak; the body was soft, and there was excessive sweating. He could not support his head firmly and forgot to smile and cry. The temperature was 37.1 C. (98.8 F.). The urine and stool were normal.

On August 20, physical examination revealed a rather poorly developed and poorly nourished child. The head circumference was 41.2 cm.; the chest circumference, 36.8 cm.; the height, 64 cm., and the weight, over 5,000 Gm. The fontanels were slightly wider open than is normal. The expression of the face

and eyes was dull. The eyelids were ptotic. Movement of the eyeballs was sluggish in all directions. The child was pale, the throat was slightly red and the tongue had a white coating. He could not support his head firmly. There were moderate sudamina on the occiput. The cardiac rate was increased. The boundary of dulness of the heart could not be determined owing to meteorism. The abdomen was swollen and tympanitic. Consciousness was a little disturbed, the state resembling that of a drunken man. The knee tendon reflexes were increased; the cremasteric reflex was positive. It was not determined whether or not the baby had disturbance of sensibility.

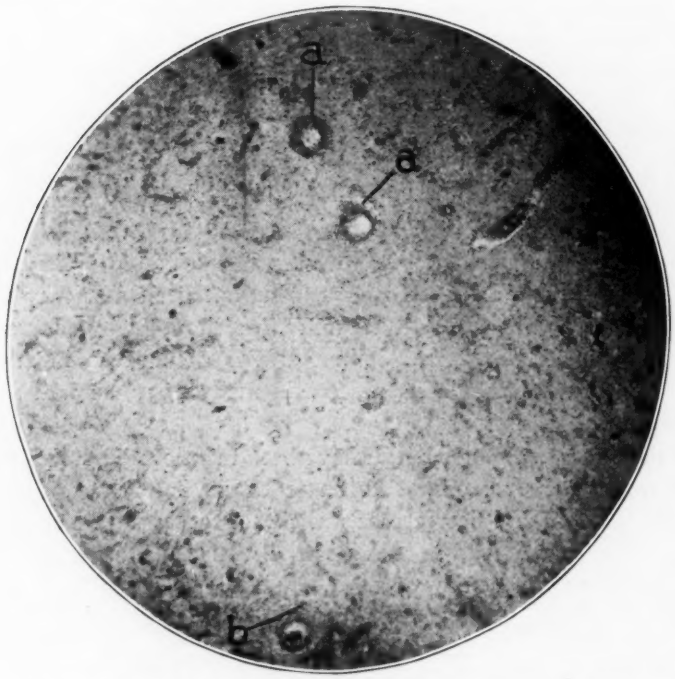


Fig. 1.—Low power photomicrograph (hematoxylin and eosin stain) of a section of the oculomotor nucleus, showing hypertrophy of the walls of the blood vessels, perivascular hemorrhages and new-formation of blood vessels: *a* indicates a perivascular ring formation with bleeding and hypertrophy of the blood vessels; *b* shows the location of the area shown in figure 2.

Examination of the eyes (by Dr. T. Miyashita of the eye clinic) revealed: moderate ptosis; moderate paralysis of the external rectus muscles; slight paralysis of the superior and inferior rectus muscles; slight paralysis of all other external muscles of the eyes; slight sensible disturbance of the corneas; an almost normal background of the eyes (although accurate examination could not be made because the baby would not fix his eyes).

I allowed the patient to continue to take breast milk and to be taken home, giving him oryzanin and medicine for the relief of the cardiac disturbance.

On August 21, the child was again admitted to the hospital, owing to sudden convulsions, which took place at 4 p. m. He was comatose. After admission

general convulsions took place continually. All the limbs were rigid, and the eyes were shut and difficult to open. Respiration was irregular. He moaned a great deal when the convulsions became stronger. The knee tendon reflexes increased. The heart rate was very slow. The fontanels were normal. At 7: 50 p. m. he flopped the right upper limb. The left upper limb was rigid. The lower limbs were movable but somewhat stiff.

On August 22 the observations of the doctor in attendance before death were as follows: Although cardiac function was good, respiration was irregular and inspiration deep. The end of the tongue was slightly cyanotic. When convulsions

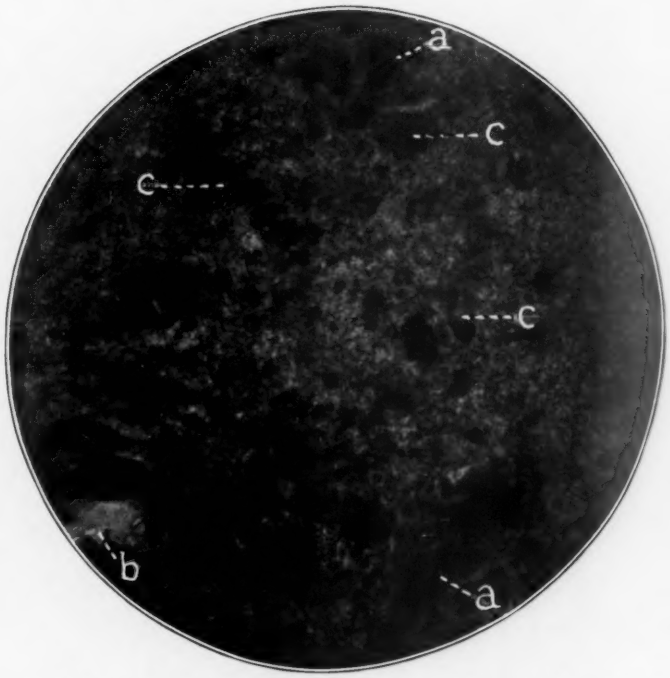


Fig. 2.—High power photomicrograph of the area designated by *b* in figure 1: *a* indicates bleeding; *b*, the lumen of a blood vessel; *c*, nerve cells, which show degeneration and seem shadow-like and structureless.

became strong, the eyes and the mouth could not be opened. The knee tendon reflex was strong, and the Babinski sign was positive. In the meantime convulsions of the masseter muscles took place, and slight opisthotonos was seen. The cardiac function was better for a little while on artificial respiration and was regular, but it gradually became weak and at last stopped during a strong attack of convulsions at 6: 30 a. m. on August 23.

*Gross Postmortem Examination* (performed by Dr. M. Otsuki).—The parent allowed necropsy to be performed only on the brain. The chief changes noted were hyperemia and edema of the meninges and hyperemia of the nuclei, the corpus striatum and the optic thalamus.

The leptomeninges and the hemispheres of the brain were hyperemic and edematous but not discolored. The leptomeninges of the base of the brain were

also hyperemic and edematous, especially at the optic commissure, but were not discolored. The gyri of the hemispheres were narrow and deep. The medullar substance was normally hard. The breadth of the lateral ventricles was normal. The choroid plexus and the ependyma were hyperemic. There were many bloody points on the section of medulla, especially in the nuclei, but no hemorrhages. The boundary between the white and the gray substance of the brain was distinct. The third and fourth ventricles were macroscopically normal. The cerebellum, pons and medulla oblongata were macroscopically normal. The leptomeninges in the region of the medulla oblongata and the spinal cord were extremely hyperemic.

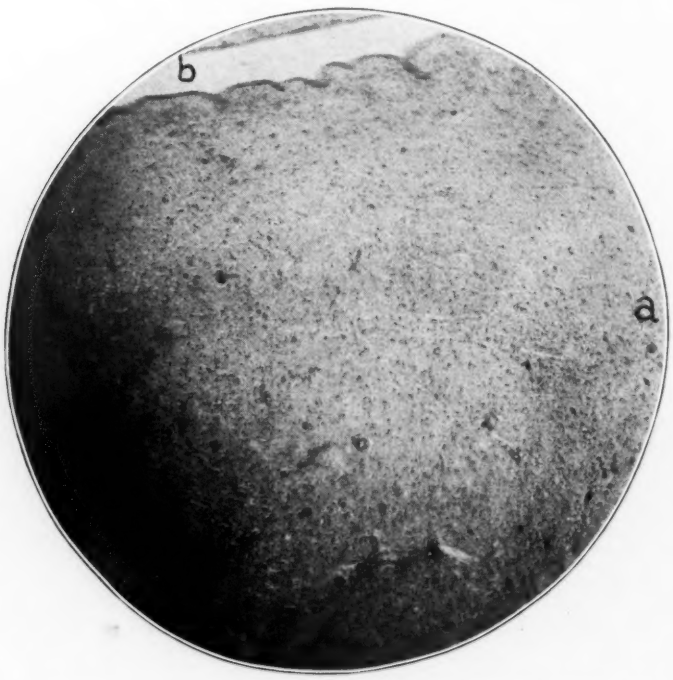


Fig. 3.—Low power photomicrograph (hematoxylin and eosin stain) of a section from the median part of the chief motor nucleus of the trigeminal nerve, showing new-formation and hypertrophy of blood vessels: *a* indicates a part of the trigeminal nerve; *b*, the aquaeductus Sylvii.

*Histologic Examination.*—The brain was put into a dilute solution of formaldehyde (1:10). Blocks from various parts after being infiltrated with the formaldehyde were well washed with running water and put into pyroxylin, after which they were dehydrated in alcohol and cut. The usual hematoxylin-eosin stain was used for general examination, and Nissl's stain was employed for the observation of changes in the nerve cells.

From the medulla oblongata to the superior colliculi the brain was cut in serial sections 20 microns thick, and every tenth section was studied.

The anterior horn of the cervical portion of the spinal cord was hyperemic, and the blood vessels were widened. In some of the sections a few hemorrhages were noted. The spinal meninges were slightly hyperemic.

Fresh hemorrhages were observed in a small area in the substantia reticularis of the medulla oblongata, ventral from the hypoglossal nucleus and lateral from the nucleus ambiguus, not far from the point where the lateral bulbothalamic tract comes out from the fasciculi of Burdach and Gowers. The ground substance of the hypoglossal nucleus was spongy and loose. In an area lateral from the hypoglossal nucleus and under the wall of the fourth ventricle there were many newly formed capillaries, and the endothelial cells of the walls of the blood vessels had dark-stained nuclei rich in chromatin and were hypertrophied. These changes gradually became slighter in the caudal direction until finally the substantia reticu-

Fig. 4.—Low power photomicrograph (hematoxylin and eosin stain) of a section in which the vagoglossopharyngeal nucleus lies, showing new-formation of blood vessels, hypertrophy and hyperplasia of the endothelial cells: *a* indicates a perivascular hemorrhage; *b*, a newly built vessel.

laris showed only hyperemia and hemorrhages. In the cranial direction, the changes became more and more intense, and the vestibular nucleus showed evidence of much injury. The nerve cells of the nucleus were swollen and round, the nucleoli had disappeared, all the nuclei were atrophied and few Nissl bodies could be seen.

Extending from the caudal border of the hypoglossal nucleus inflammation was noted in a group of structures including the motor and sensory nuclei of the vagus and glossopharyngeal nerves, the posterior longitudinal fasciculus, Deiters' nucleus, the nucleus of the middle vestibular nerve and the nucleus intercalatus. There was prominent new formation of capillaries as well as hypertrophy and

hyperplasia of the endothelial cells of the vascular walls. Hemorrhages and hyperemia were distinct.

The nerve cells of the motor nucleus of the vagus and glossopharyngeal nerves were swollen; the nuclei were shrunken and irregular in form and their position in the protoplasm was not normal; the nucleoli had disappeared. The cells had become eosinophilic. The Nissl bodies had almost disappeared, but some remained, irregularly distributed in the borders of the cell bodies. Where injury was most severe, the nerve cells were shadow-like and tended to disappear. The sensory nucleus of the vagus and glossopharyngeal nerves had suffered less than the motor nucleus, and shadow-like cells were not seen.

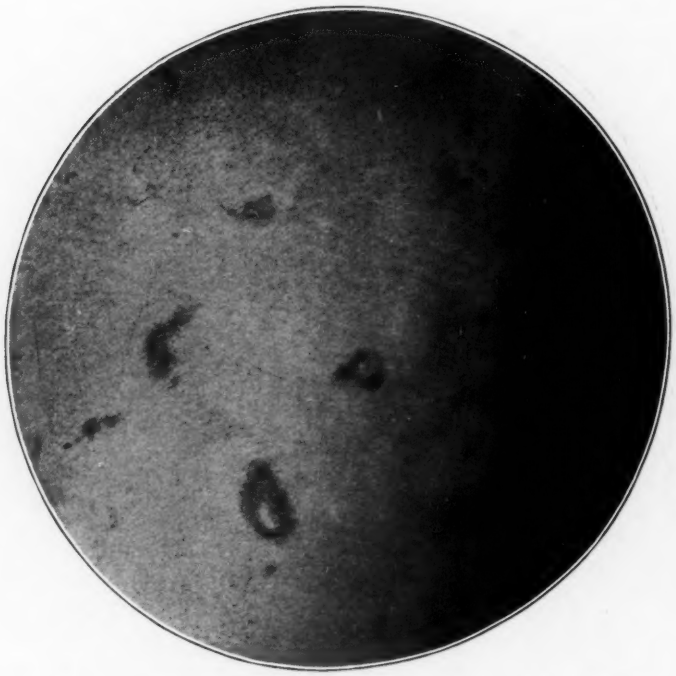

Fig. 5.—Low power photomicrograph (hematoxylin and eosin stain) of a section of the corpus striatum, showing perivascular hemorrhages.

The center of this inflammatory area was the motor vagoglossopharyngeal nucleus, and the farther one progressed from this center, the less intense was the injury.

The vestibular nucleus had also undergone extensive injury. The median vestibular nucleus had suffered more than the lateral and spinal nuclei. Some of the nerve cells of the median nucleus were swollen or broken, and others had become shadow-like or had disappeared. There were many cells with indistinct structure and shrunken nuclei. In those cells, although the nuclei were distinctly stained, the Nissl bodies had disappeared. Newly formed capillaries and hyperplasia and hypertrophy of the endothelial cells of the vascular walls were observed, as in the vagoglossopharyngeal nucleus. There were hemorrhages around the vessels. The ground substance was loose and devastated, but not so markedly as in the vagoglossopharyngeal nucleus.

The substantia reticularis, the hypoglossal nucleus, the eminentia teres, the nucleus intercalatus, the nucleus alae cinereae and the nucleus of the spinal root of the trigeminal nerve suffered almost the same grade of injury. However, this injury did not continue as far as the abducens nucleus.

The changes in the abducens nucleus were not so distinct as those just described. There were a few hemorrhages and some hyperemia. There was slight cellular infiltration around some of the blood vessels. The ground substance was loose in places. Almost all of the nerve cells were intact, but some of them were swollen and showed shrunken nuclei and disappearance of the nucleoli. In some sections many of the nucleoli had disappeared, the nuclei were shrunken, the form of the cells was destroyed and they were eosinophilic. The nuclei were not in their normal position but stood on the edges of the cell bodies, and the Nissl corpuscles gathered irregularly on the borders of the cell bodies. In general, the pericellular spaces were broad.

The substantia reticularis around the abducens nucleus, especially near the chief motor nucleus of the trigeminal nerve, showed much new formation of capillaries and hypertrophy and hyperplasia of the endothelial cells of the blood vessels. There were many hemorrhages. The nerve cells of the lateral and median vestibular nuclei had suffered a good deal of injury. Many of them were swollen, and the Nissl corpuscles gathered on the borders of the cell bodies. The nucleoli had disappeared, and the cell bodies had become homogeneous and were irregular in form. Here and there in the pyramids were a few hemorrhages and hypertrophy and hyperplasia of the endothelial cells of the blood vessels.

The nucleus of the facial nerve was intact. However, in the meninges around the exit of the nerve there was a fairly wide hemorrhagic area, and considerable bleeding was seen in the fibers of the nerve after it had circled the abducens nucleus and as it passed the substantia reticularis. Moreover, hemorrhage was seen in the tectospinal tract in the sections in which the facial nerve lay.

Along the chief motor nucleus of the trigeminal nerve from the joining of the brachia conjunctiva to the aqueduct of Sylvius, especially mediad from this nucleus, there was much formation of new capillaries as well as hyperplasia and hypertrophy of the endothelial cells of the blood vessels and hemorrhage. The changes were distinct near the oculomotor nucleus.

The motor nucleus of the trigeminal nerve was not so much damaged, but near the center of inflammation many of the nerve cells were swollen, the nuclei were shrunken, the nucleoli had disappeared, the nuclei did not lie in the center of the cells, and the cells were eosinophilic. Inflammation spread from this area over the joining of the brachia conjunctiva ventral to the lemniscus, and in some sections to the nucleus lemnisci lateralis. The superior olivary nucleus lies in this area and was affected by this inflammation but did not suffer much injury. Many of the nerve cells were swollen; the nuclei were shrunken, and some of the nucleoli had disappeared. In many of the cells the Nissl corpuscles gathered in the border of the cell body, and in some these corpuscles were not observed. Caudad from the motor nucleus of the trigeminal nerve and in and outside of the tegmentum there was a small area of hemorrhage and hyperemia.

In the lamina quadrigemina there was considerable formation of new capillaries as well as hyperplasia of the endothelial cells of the blood vessels and slight hemorrhage at the base of the inferior colliculi. These changes gradually became slighter toward the dorsal surface. The superior colliculi showed the same changes, though to a greater extent. Most of the nerve cells were eosinophilic, their nuclei were shrunken and the nucleoli had disappeared. Inflammation spread laterally

from this area to the brachia conjunctiva. However, the center of inflammation in this region was the oculomotor nucleus.

The trochlear nucleus was the center of a small area of inflammation. As in the other inflammatory areas, there were new-formed capillaries as well as hyperplasia and hypertrophy of the endothelial cells of the blood vessels. There were some nerve cells in which the protoplasm could not be differentiated from the ground substance. Even in the cells in which the nucleus was distinct the nucleolus had disappeared and the nucleus was at the edge of the cell body. It is curious that there was no hemorrhage. The nucleus dorsalis tegmenti accessorius and the nucleus lateralis aquaeducti, which lie near the trochlear nucleus, were involved by the inflammation, but the damage to these nuclei was much slighter than that to the trochlear nucleus. There were a few hemorrhages in and about the posterior longitudinal fasciculus. The damage to the trochlear nucleus was fairly severe.

The oculomotor nucleus was the most severely damaged of all the structures examined. The ground substance was very loose. Where the injury was worst, the nerve cells could not be seen under low power magnification; with high power magnification they became visible but were seen with difficulty, resembling shadows of cells. The nuclei were shrunken; they had lost their round form and were irregular and had moved to the borders of the cells. The cells had lost their original form and had become irregular and swollen. It was difficult to differentiate the ground substance from the cell protoplasm. The nerve cells which had suffered only slight injury were edematous, swollen and round. The dorsal nucleus was more markedly affected than the ventral nucleus. Half of the nerve cells of the dorsal nucleus had lost their nucleoli, while most of the cells in the ventral nucleus retained their nucleoli. Nissl's corpuscles had disappeared in the cells of the dorsal nucleus but were seen in some of those of the ventral nucleus, gathered on the edges of the cell bodies. Formation of new capillaries was distinct. The nuclei of the epithelial cells of the blood vessels stained deeply and showed hypertrophy and hyperplasia. The lumens of some of the blood vessels were irregular and tortuous. Such changes in the blood vessels were seen near the wall of the fourth ventricle. Hemorrhages were distinct and were observed about almost all of the vessels.

Inflammation extended dorsally from this area to the corpora quadrigemina, ventrally to the thalamo-olivary tract and laterally to the tectospinal tract. The changes in the posterior longitudinal fasciculus were pronounced. The pes pedunculi, locus niger and red nucleus were also involved, though not markedly. They showed hypertrophy and hyperplasia of the endothelial cells of the blood vessels and occasional slight hemorrhages.

The corpus striatum showed many hemorrhages and much hyperemia. In the optic thalamus hyperemia was as distinct as in other areas, and in some sections there were a few hemorrhages. The caput nuclei caudati showed no distinct changes. In the dentate nucleus and several other parts of the cerebellum (the tonsilla cerebelli, the superior and inferior semilunar lobules, the anterior and posterior portions of the quadrangular lobe and the vermis), there were a few small hemorrhages and much hyperemia in the marrow and in the meninges. The dentate nucleus was pale, and its ground substance was loose.

In the upper part of the cortex of the sylvian fossa, the meninges were markedly edematous, and the tissues were swollen. The parenchyma of the cortex was extremely hyperemic, and in the marrow also there were many hyperemic areas. There was much edema around some of the vessels. In the lower part of the

cortex of the sylvian fossa, a slight degree of hyperemia was seen in the marrow, but none was noted in the gray substance.

In the superior frontal gyrus there was hyperemia in some parts of the marrow substance but none in the gray substance. The changes in the meninges were the same as those in the upper part of the cortex of the sylvian fossa. In the inferior frontal gyrus the changes in the meninges were similar. Some of the vessels were edematous.

In the motor speech center of the cortex the meninges were extremely hyperemic, and a few hemorrhages were seen. In the sensory speech center the meninges were markedly edematous in places, where as usual there was also much hyperemia. There was slight hyperemia in the marrow. In the optic center the meninges and the marrow were hyperemic.

The cornu ammonis was only slightly hyperemic.

The choroid plexus was extremely hyperemic, and some hemorrhagic areas were seen.

*Summary of Histologic Observations.*—The oculomotor nucleus, the nucleus of the trochlear nerve, the median side of the chief motor nucleus of the trigeminal nerve and the vagoglossopharyngeal nucleus were the centers of inflammation, where hyperemia and hemorrhage were pronounced. The changes of the oculomotor nucleus were the most severe; next in intensity were those of the median side of the chief motor nucleus of the trigeminal nerve, and next those of the vagoglossopharyngeal nucleus. The inflammation was not limited to these nuclei but spread to the neighboring areas, such as the substantia reticularis, the posterior longitudinal fasciculus, the medial lemniscus, the corpora quadrigemina and the motor nucleus of the trigeminal nerve.

## COMMENT

Where the hemorrhage and hyperemia were extreme, the endothelial cells of the vascular walls were hypertrophied and hyperplastic, and newly formed capillaries appeared. The nuclei of such endothelial cells were rich in chromatin and stained deeply and distinctly. It seems, therefore, that the walls of the blood vessels had been injured before bleeding occurred and that the hemorrhage was the consequence of injury to the endothelial cells. The hemorrhage was almost all fresh and must have occurred shortly before death. It was probably the direct cause of death. The acute changes in the nerve cells must have occurred after the onset of the bleeding. It is of interest that the nuclei which were the center of inflammation were all situated near the wall of the fourth ventricle and that all of the nuclei which lay far from the ventricular wall were intact. The hemorrhage and hyperemia of the meninges, the choroid plexus and other parts of the brain were not the main changes but merely accessory manifestations.

## CONCLUSION

The patient whose brain I examined presented a typical syndrome of so-called breast milk intoxication. Not only clinically but histo-

logically the condition was polioencephalitis haemorrhagica superior (or inferior) acuta (C. Wernicke). Therefore, according to these observations, so-called breast milk intoxication is polioencephalitis haemorrhagica superior (or inferior) acuta.

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# Case Reports

## CONGENITAL ATRESIA OF THE ESOPHAGUS WITH TRACHEO-ESOPHAGEAL FISTULA

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In reviewing the literature on congenital atresia of the esophagus, almost every author begins with Sir Morell Mackenzie's [1] collection of 62 instances compiled in 1884 for the report of his own single case. According to Mackenzie, the first recorded case was that of Durston in 1670. In 1861, Hirschsprung [2] collected 10 cases from the literature and reported 4 new cases. In 1913 and 1918, Brennemann [3] reported 7 cases seen in a period of five years. In 1919, Plass [4] collected the reports of 136 cases of esophageal atresia. Since then, Rosenthal [5] has assembled 85 additional cases, of which 61 were associated with tracheo-esophageal fistula and 14 were cases of atresia occurring independently. In the 10 remaining cases the presence or absence of fistula was not established by autopsy, although the clinical findings pointed to its existence in the majority of the instances as well as to the presence of atresia in all. Rosenthal reported 8 cases, raising the total found at the time of his paper (1931) to 255 cases in which congenital esophageal atresia was definitely established. In 215 of these cases a tracheo-esophageal fistula was present, and in 40 it was definitely absent. Since

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the cases described by Rosenthal, others have been reported by Imperatori,[6] Soer,[7] Sussman,[8] Graham,[9] Thompson,[10] Bohrer[11] and Trump.[12] This brings the apparent total to 262, and since seeing the case reported here in October, 1931, there have been 4 other cases in the city of New Orleans, which so far as we know have not yet been recorded.

This, however, cannot be taken as the number of cases that have occurred, for it is obvious that many recognized cases have not been reported, and there can be no doubt that some have been overlooked.

Shukowsky and Baron[13] reported a case in 1912 as the only one which they had seen in a hospital experience with 50,000 new-born infants. Cautley[14] mentioned that his case, in 1917, was the first that he had seen in twenty-five years of practice, mainly among children.

On the other hand, Hirschsprung saw 4 cases in seven months and later reported 5 others, and Brennemann reported his 7 cases in five years. These experiences, with 8 cases reported by Rosenthal and the 5 which have occurred in New Orleans within fifteen months, seem to indicate that the anomaly is less rare than was formerly supposed.

The variation in the frequency with which these cases occur in the experience of various reporters is quite logically explained in a suggestion by Brennemann. He called attention to the fact that on seeing a rare case a clinician commonly becomes interested in finding others and is soon rewarded in his search. He is equally logical in his assertion that the diagnosis is easy for any one who has the condition in mind or who has ever seen a case.

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14. Cautley, Edmund: Malformation of the Esophagus, Brit. J. Child. Dis. **14**:1, 1917; sited by Brennemann.[3b]

SYMPTOMS

The uniformity of the symptoms described in the numerous case reports is striking, the histories varying little, if at all, in essentials. There is nothing remarkable about the infant during the first twenty-four or forty-eight hours, but as soon as attempts are made to give it water or food, the typical signs begin to appear. There seems to be a unanimity of opinion that prior to these typical signs the first sign is a constant but slight flow of saliva from the mouth. Usually, because of the mixture with air from the lungs, the saliva is frothy. If attempts are made to encourage nursing or if water is given, the infant "will swallow once or twice without any trouble. With every further attempt at swallowing, the fluid will return in jets alongside of the nipple and through both nostrils. The child is now compelled to breathe with the mouth, nose, and pharynx full of liquid. It suddenly stops nursing, its eyes become fixed, it rapidly turns blue, and then struggles to empty the lungs by coughing." Thus, Brennemann sketches the early picture of every case.

At this stage death from drowning may occur, but, according to Brennemann, not until the infant's defense is weakened, as it is in the later stages. The most plausible explanation of the protection is that a greater part of the fluid may be drained from the trachea into the stomach by way of the tracheo-esophageal fistula.

This chain of symptoms occurs with each effort to nurse, or on the administration of fluid, and in the interval the infant lies in a state of prostration. It recovers, only to go through the paroxysm after each attempt at feeding.

The weight naturally falls steadily, and the infant rapidly becomes dehydrated. The anterior fontanel is depressed; the skin becomes dry and later parchment-like, and the tissues lose turgor. The upper part of the epigastrium is usually greatly distended and tympanitic. Especially is this so when a tracheo-esophageal fistula is present. The distention is caused by air that reaches the gastro-intestinal tract from the lung. This abdominal distention caused by air has become generally recognized as a reliable clinical sign by which the presence of a tracheo-esophageal fistula can be detected, and it was especially emphasized by Brennemann in both of his communications.

For the first few days the stools show meconium, but later they become scant and consist of bile-stained mucus, as seen in starvation. The temperature may be normal or subnormal, but as inanition progresses, the temperature usually rises. It also rises because of bronchitis and bronchopneumonia, which invariably develop as a result of the aspiration of food during each attempt at feeding. The periods

of survival noted in a series of cases reviewed by Hirsch,[15] with the numbers succumbing at various ages, are as follows: stillborn, 5; died on first day, 15; on second day, 18; on third day, 13; on fourth day, 14; on fifth day, 12; on seventh day, 7; on eighth day, 6; on ninth day, 4; on tenth day, 3; on eleventh day, 4; on twelfth day, 1; on thirteenth day, 1, and on fourteenth day, 1.

The diagnosis is usually verified by the obstruction encountered when an attempt is made to pass a catheter, or by a roentgenogram which, following the introduction of radiopaque mediums, shows the upper portion of the esophagus ending in a somewhat dilated culdesac a few centimeters below the clavicles.

## REPORT OF A CASE

*History.*—A white female infant, the second child of young and healthy parents, was born at full term after normal labor, and weighed 7 pounds (3,175.14 Gm.). The older child was normal. It was noticed that the infant had difficulty in nursing and regurgitated the breast milk almost immediately after taking it. The regurgitation of milk and frothy mucus was accompanied by attacks of cyanosis, tetanic movements of the arms and spasmodic rigidity that involved the entire body. Intracranial hemorrhage was thought of, but evidences of obstruction soon indicated that hemorrhage was not responsible for the symptoms. Because of progressive loss of weight and rapid dehydration, the child, then 5 days old, was brought from its home, sixty miles away, for roentgenologic examination. When, preparatory to making a gastro-intestinal study, effort was made to pass a catheter for introducing barium sulphate, an obstruction in the esophagus was encountered about 10 cm. from the lips. An immediate fluoroscopic examination revealed the catheter in a completely obstructed esophagus. A small amount of barium sulphate was injected, and the roentgenogram shown in figure 1 was taken.

In addition to the clearly defined obstruction in the esophagus, the barium sulphate was seen in the left lung. This finding, together with the fact that the stomach and upper intestinal tract was greatly distended with air, indicated that the atresia was of the predominating type in which a tracheo-esophageal fistula is associated. In emphasizing the distention of the stomach with air as a pathognomonic sign of a tracheo-esophageal communication, Brennemann [3a] reported audible respiration through a catheter inserted into the stomach after a gastrostomy.

*Treatment.*—With the establishment of the diagnosis came the realization of a hopeless prognosis. We were fully aware that temporizing operations have never been known to accomplish anything. Nevertheless, it was decided to resort to surgery on the chance that the unexpected might occur. Because of the existence of the communication between the stomach and trachea, gastrostomy was not considered. Death from drowning has resulted almost immediately in every case as soon as attempts have been made to introduce liquid food through a gastrostomy

15. Hirsch, I. S.: Congenital Atresia of the Esophagus, J. A. M. A. **76**:1491 (May 28) 1921.

tube. Surgical closure of the cardiac end of the stomach has been considered repeatedly and actually done [16] as a rational procedure in such cases, but surgeons have been reluctant to close the passage because it adds to the difficulties of any radical operation which might subsequently be performed.

After consultation, jejunostomy was performed the same day by Dr. Alton Ochsner, of the department of surgery, following the usual measures to overcome dehydration. The operation was a surgical success but a pediatric failure. All efforts to nourish the seriously undernourished infant under such adverse physiologic and anatomic handicaps ended in the usual merciful death two days later.

Fig. 1.—Congenital atresia of the esophagus. The barium sulphate shown in the right lung has passed through the fistulous opening between the esophagus and the trachea. The marked distention of the stomach and intestines is caused by air which has passed through the communication between the trachea and the cardiac end of the stomach.

Thoracic surgery may some day include an operation to correct this condition, but there will still be obstacles to overcome. It will probably continue to be difficult, if not impossible, to nourish a new-born infant under such circumstances.

16. Richter, H. M.: Congenital Atresia of the Esophagus: An Operation Designed for Its Cure, Surg., Gynec. & Obst. **17**:397 (Oct.) 1913.

Then the possibility of overcoming the bronchopneumonia, which is an invariable complication before the diagnosis is made, will always be remote. Moreover, the presence of other anomalies is frequent in these unfortunate infants. Brennemann discussed these obstacles in recording his extensive experience. Nothing has occurred since to change this impression, though Rosenthal insists that the coexistent anomalies are usually compatible with life, and that their occurrence should not discourage surgical intervention designed to correct the esophageal defect.

*Necropsy.*—Owing to the obvious demand for a more thorough dissection than could have been carried out in the routine autopsy, the viscera were removed and preserved intact for subsequent study. It was only from this point that one of us (H. C.) had connection with the case, the viscera (then in Kaiserling's solution) being submitted for examination. The organs were removed with care to avoid disturbing their relationships. The operator dissected upward in the

Fig. 2.—Viscera removed at autopsy. The pin pierces the stomach wall and passes through the cardiac end of the stomach, through the communication to the trachea and out. The esophagus ending in a culdesac is seen below the trachea.

neck, freeing in one mass the lower part of the pharynx, tongue, larynx, trachea, esophagus and structures immediately surrounding them. These organs, after transection of the pharynx, were lifted away in continuity with the thoracic and abdominal viscera. The pelvic structures were not included, and it is therefore impossible to present any specific statement concerning the anatomy of the genitourinary passages and terminal region of the intestinal tract; the clinical examination, however, excludes the existence of major maldevelopments such as atresia ani and persistent cloaca.

The detailed dissection of the tracheo-esophageal region was directed not only to the exposure of the structures immediately involved in the malformation, but also to the preservation of the surrounding parts, particularly the neighboring vascular trunks (since aberrant vessels have been regarded by several writers as agents effecting the abnormal development of the trachea and esophagus). The

significant findings in the dissection of the tracheo-esophageal region are illustrated in figure 4.

An extent of about 10 mm. of the esophagus was found to be constricted, this region being narrowed from above and below to a minimum transverse dimension

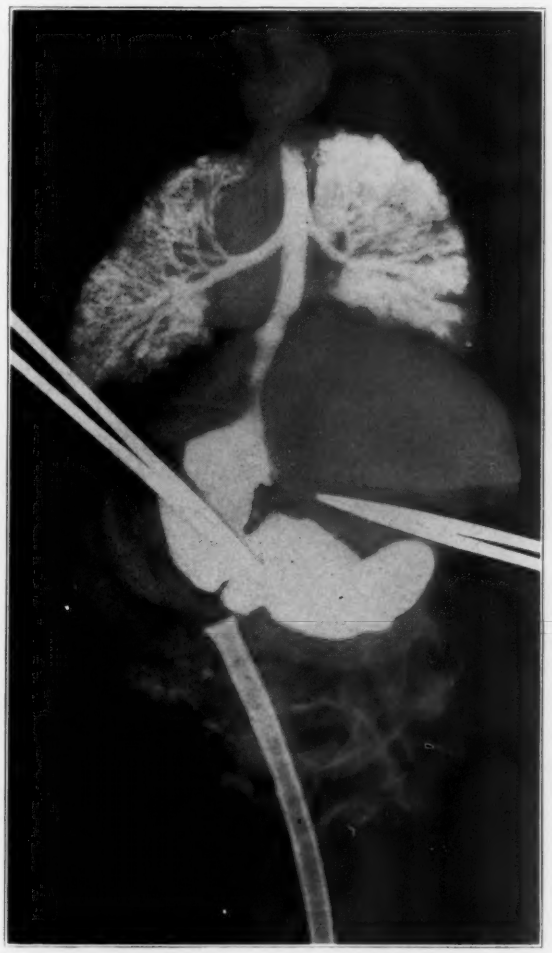

Fig. 3.—The viscera, following an injection of iodized poppy seed oil 40 per cent. The left hemostat clamps the pylorus, and the right clamps the opening in the stomach which was made by the transfixing pin shown in figure 2. The jejunostomy tube is shown below.

of 2 mm. The minimum diameter was attained at a level 15 mm. above the crotch of the tracheal bifurcation. Above the atretic region the esophagus was distended and its wall hypertrophied. On dividing the trachea along the anterior midline the communication with the lower esophageal segment was found to lie about

10 mm. above the crotch of the tracheal bifurcation, the orifice being of crescentic form and guarded inferiorly by a free lip (fig. 4).

Neither the trachea nor the larynx exhibited gross abnormality, barring the fistula, and examination of histologic sections cut in the sagittal plane failed to disclose any departures from the normal minute organization of these structures. In view of the interest attached to the esophageal musculature in these cases (Keith [17]), it should be noted that the lower esophageal segment contained smooth muscle only, and that the characteristic disposition of layers was disturbed. Slightly below the level of the fistula, for example, there was an area showing two layers, as is typical, but these were reversed in direction—the inner one being longitudinal and the outer one circular. Elsewhere in the vicinity of the fistula, including the lip guarding it, were bundles of muscle irregularly disposed. The upper segment contained both smooth and skeletal muscle, the two varieties being about equally represented, mixed in bundles composing the two typical coats. The upper segment showed no further points of interest beyond the fact that its wall

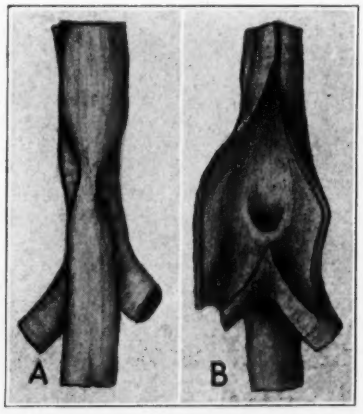


Fig. 4.—Dissection of the esophagus and trachea, actual size: *A*, dorsal aspect, showing the division of the esophagus into upper and lower segments by the interval of atresia; *B*, ventral aspect, the trachea being opened in the midline to expose the orifice of the fistula leading into the lower esophageal segment.

was thickened, except in the extreme upper part, both muscular and fibrous layers participating. The narrowed zone, under histologic examination, proved to exhibit a true atresia, in contradistinction to stenosis, in that this region consisted of a band composed only of white fibrous connective tissue and smooth muscle, coursing longitudinally. No vestige of an epithelial lining was detected in this region, though a search was made for epithelial cords and nests. It may be noted, however, that glandular alveoli extending from ducts opening into the nearby patent segments were directed toward the atretic interval. The lining epithelium of the trachea was not well preserved, owing perhaps to exploratory probing. The epithelial remnants suggested that the entire trachea was lined, typically, with stratified columnar epithelium extending to the margin of the fistula, to be succeeded here by the stratified squamous epithelium characteristic of the esophagus.

17. Keith, Arthur: Constrictions and Occlusions of the Alimentary Tract of Congenital or Obscure Origin, Brit. M. J. **1**:301, 1910.

The gastro-intestinal tract displayed nothing of note beyond distention of the jejunum and ileum with gas. The jejunostomy tube had been inserted 10 cm. below the termination of the pyloric sphincter. Sections of the esophagocardiac and pyloroduodenal junctions were negative as to signs of stenosis or other abnormality. Lobation of the lung was normal, and sections yielded only the expected finding of lobular pneumonia. The heart and great vascular trunks, kidneys, suprarenal glands, spleen, pancreas and liver showed no gross evidences of abnormality.

## COMMENT

*Origin of the Malformation.*—Attention may be directed to a loose usage of the term etiology as applied in many of the published accounts of this and other developmental defects. It should be recognized that certain of the suggested explanations of tracheo-esophageal fistula deal solely with a conjectured aberrant developmental history, and that even if these correctly describe the sequence of perverted embryologic events, they are not concerned with actual causation. To determine the true etiology a search must be made for the agencies ultimately responsible for the abnormal development. In this case we have been able to secure neither a family history nor a maternal clinical history, which might have suggested one or more such factors. The agencies predisposing to the anomaly are to be sought either in the reproductive cells from which the child was produced or in an unfavorable intra-uterine environment obtaining during the critical early period of embryonic life (Cummins [18]). The anomaly is an expression of a fundamental biologic incapacity, the effects of which are frequently seen in the occurrence of multiple defects in the same subject. Thus, in the series of esophageal atresias collected by Plass there are 94 cases in which the presence or absence of other defects has been noted, and of these, 59 showed anomalies additional to the atresia. The most common associated defect was atresia ani, found in 24 cases. Whatever the specific nature of the etiologic agencies, it is apparent that they operate frequently to handicap the development of the embryo in regions other than the tracheo-esophageal territory. With these points in mind it should be clear that the following comments dealing with the reconstruction of the development of the anomalous tracheo-esophageal anatomy are in no sense a consideration of etiology. Various suggested reconstructions of this developmental history have been proposed. They were collected and ably discussed by Rosenthal; [5] hence a detailed review is unnecessary here.

In the normal development of the trachea and esophagus it is observed that the epithelial mold of the entire respiratory tract arises from the ventral wall of the primitive foregut, its differentiation being first indicated in the embryo of 3 mm. length. Separation of the

18. Cummins, Harold: Bodily Malformations in the Light of Embryology, Blumer's Practitioners' Series, New York, D. Appleton and Company, 1932, vol. I.

tracheobronchial rudiment from the overlying foregut (esophagus) is rapidly effected. Between them, first evident caudally, there appears on each side a longitudinal infolding. With approximation of the two infoldings, which apparently progress at the same time cranially, the respiratory tract lengthens and branches at its free end. The definitive mutual relations of the two tracts are attained by the time that the embryo has grown to a length of about 11 mm.

When considering the developmental origin of a typical esophageal atresia combined with tracheo-esophageal fistula, as exemplified in the present case, it is well to review the varieties of malformation to which the esophagus is subject. The following classification (adapted from Ballantyne,[19] Birnbaum [20] and Phelps [21]) is inserted as a self-explanatory illustration of the diverse malformations affecting the esophagus. To ignore the existence of this wide range of defects, rare though some examples are, is to overlook an important item bearing on the genesis of the typical case. Their occurrence contraindicates, it would seem, any explanation which centers about a local mechanical causal factor to the exclusion of the less tangible developmental incapacity which is stressed here.

*Developmental Defects of the Esophagus.*—These may be listed as:

A. Involvement of the entire passage
   1. Stenosis
   2. Total atresia (reduced throughout to a solid cord)
   3. Agenesia (no detectable vestige of the structure)
   4. Doubling of the whole length of the passage

B. Regional involvements
   1. Stenosis (single or multiple stenotic intervals)
   2. Atresia (either by the narrowing of an interval or by the presence of a barrier fold or membrane in an esophagus otherwise normal)
   3. Agenesia (no detectable remnant of a restricted interval)
   4. Fistula communicating with trachea or a primary bronchus
      *a.* Esophagus otherwise normal
      *b.* Esophagus divided into upper and lower segments by a regional stenosis, atresia or agenesia, the fistula being usually single and uniting the lower segment with the trachea
   5. Doubling in a short extent
   6. Diverticula
   7. Cysts

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19. Ballantyne, J. W.: Manual of Antenatal Pathology and Hygiene, Edinburgh, W. Green & Sons, 1904.

20. Birnbaum, R.: Klinik der Missbildungen und kongenitalen Erkrankungen des Fötus, Berlin, Julius Springer, 1909.

21. Phelps, K. A.: Congenital Anomalies of the Esophagus with a Report of Nine Cases, Ann. Otol., Rhin. & Laryng. **39**:364, 1930.

Rosenthal [5] pointed out that the developmental explanations of the typical esophageal atresia, with or without fistula, fall into three main classes: (1) It has been suggested that the malformation arises by retention of an assumed normal atresia which is typically transitory. (2) Abnormal deviations of the septum dividing the esophagus and trachea have been postulated. (3) Compression of the tracheo-esophageal structures by blood vessels or by the heart figures as a more recent speculation. Rosenthal himself advances a quite different suggestion, with which we are in complete agreement. He considers that the anomaly is to be explained as a result of a primary deficiency in the developmental capacities of the tissues concerned, and believes that such mechanical explanations as those which concern deviations of the cleavage of the pulmonary tract from the esophagus do not reach this fundamental seat of disturbance, though they are admittedly of descriptive value. Other proposals appear to be quite far from arriving at the explanation; the assumption of a normal epithelial occlusion is no longer tenable, and compression by blood vessels or the heart is not a demonstrable source of the maldevelopment.

The frequency of other malformations associated with tracheo-esophageal defect has already been mentioned as a matter of prime importance in considering the origin of the defect. This situation alone should be sufficient reason to question the significance of any agency identified with purely mechanical local disturbances in the growing embryo. Furthermore, it must not be forgotten that the typical case has close relatives, for example in the form of total agenesia, atresia and stenosis; an explanation advanced for the typical case should be in harmony with the related conditions. Rosenthal credited Streeter, the embryologist, with a personal communication suggesting an analogy between tracheo-esophageal defect and spina bifida. Just as the neural tube is not initially closed on its dorsal aspect but becomes so by proliferation of cells along the margins, with separation from the now overlying integument, so the separation of trachea and esophagus is effected by entodermal proliferation along the lateral borders of the primitive intestine. Interruption of the closing process in the neural tube gives rise to spina bifida, and in the primitive foregut to tracheo-esophageal fistula. It is suggested that the esophageal atresia may be due to a similar developmental deficiency of the entoderm on the dorsal wall of the foregut. We believe that the analogy can be carried further, matching the varieties of tracheo-esophageal defect with the varying regional involvements in spina bifida. Tracheo-esophageal fistula and atresia are prevailingly situated at the same general level as is spina bifida. The total involvements of the esophagus may be compared to total spina bifida. In neither malformation is a mechanical explanation of greater service than to provide a description of the *effects* observed in a focus of developmental deficiency.

# BLINDNESS IN WHOOPING COUGH

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Loss of sight in a child always attracts attention. This is especially true when the blindness occurs during the course of, or subsequent to, an infectious disease. Likewise, in these cases serious ocular manifestations are much more common in childhood. In whooping cough, a wide variety of conditions present themselves, ranging from subconjunctival hemorrhage, ecchymosis of the eyelid and bleeding from the surface of the conjunctiva, producing the so-called "bloody tears," [1] to such serious manifestations as exophthalmos from retrobulbar hemorrhage,[2] bleeding into the anterior chamber,[3] circulatory disturbances and detachment of the retina [4] and embolism of both central arteries.[5] Functional disturbances without ophthalmoscopic findings, such as total blindness, hemianopia and mind blindness associated with involvement of the cranial nerves, have also been reported.[6]

Amaurosis caused by whooping cough is not only exceedingly rare, but usually transitory in nature. Such thorough observers as Henoch [7] and Sticker [8] failed to note this complication in their treatises on pertussis. On the other hand, Loomis [9] in his article on the subject, stated

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Read before the Brooklyn Pediatric Society, Nov. 23, 1932.

From the Kingston Avenue Hospital for Contagious Diseases, Brooklyn, and the Department of Hospitals, New York City.

1. Trousseau, quoted by Rolleston, J. D.: Acute Infectious Diseases, New York, Physicians and Surgeons Book Company, 1925, p. 117.

2. Cabannes and Mantoux: J. de méd. de Bordeaux **101**:215, 1924.

3. Warner: J. Ophth. & Oto-Laryng. **5**:150, 1893.

4. Landesberg: M. & S. Reporter **43**:248, 1880.

5. Teillais: Rec. d'ophth. **17**:662, 1895.

6. (*a*) Silex: Berl. klin. Wchnschr. **42**:841, 1888. (*b*) Fritsche: Jahrb. f. Kinderh. **29**:380, 1889. (*c*) Troitzky: ibid. **31**:291, 1890. (*d*) Baginsky: München. med. Wchnschr. **54**:147, 1907.

7. Henoch: Vorlesungen über Kinderkrankheiten, ed. 2, Berlin, A. Hirschwald, 1903, p. 429.

8. Sticker: Keuchhusten, in Nothnagel, C. W. H.: Handbuch der speziellen Pathologie und Therapie, Vienna, A. Hölder, 1896, vol. 4, sect. 2, pt. 2, p. 25.

9. Loomis, quoted by Knapp: Arch. Ophth. & Otol. **4**:448, 1874.

that blindness in whooping cough had been observed, and Steffen [10] discussed a case in which disturbances in the acuity of vision developed during paroxysms. Sebregondi [11] also noted temporary blindness with each paroxysm in his patient. For further cases in the literature, the reader is referred to the accompanying table.

Certain definite conclusions can be drawn from the reviewed literature. In the seventeen published reports of blindness in whooping cough from 1870 to 1930, a total of twenty cases have been described. Thirteen of the patients were females and seven males. The age incidence ranged from 19 months to 40 years, although only three occurred after adolescence. The duration of whooping cough preceding blindness was from one week to four months. The pupils reacted to light in about one half of the patients, whereas in the other recorded cases, they were fixed. The eyegrounds showed normal findings in seven cases, papilledema in four, optic neuritis in five, choroiditis in two, retinal ischemia in one, and in one these findings were unrecorded. Fifty per cent showed other cerebral manifestations. The amaurosis cleared up in from three days to nine months, and only two patients remained permanently blind.

## REPORT OF A CASE

*History.*—V. C., a white boy, aged 6 years, was admitted on Aug. 3, 1932, to the Kingston Avenue Hospital for Contagious Diseases. On admission, the child showed no elevation of temperature, pulse or respiration rate. He appeared extremely drowsy and was unable to see objects when aroused. He had the typical severe paroxysms and emesis of pertussis.

The patient was the oldest of three children. The parents gave no history of syphilis, diabetes, tuberculosis, migraine or other constitutional or hereditary diseases. The other members of the family were apparently normal. The birth history showed a normal delivery with no complications. He was breast fed until 3 months of age, walked at 12 months and talked at 14 months. His development and habits were normal. No mental or visual disturbances had been noted until the present illness. At the age of 11 months, he had a so-called "grip attack," and at 4½ years, a tonsillar diphtheria without complication or sequelae. In April, 1932, he had varicella, and in June, 1932, measles without complications.

During the first few days in July, 1932, the patient complained of rhinorrhea and an incessant dry cough which was followed by epistaxis on one occasion. These symptoms became progressively worse. By July 4, the child had from three to five daily severe paroxysms with typical whoop and emesis. The family physician diagnosed the condition as pertussis. Two weeks later, on July 18, the boy showed difficulty in breathing. The temperature was 103 F. The family doctor made a diagnosis of bronchopneumonia complicating whooping cough, but saw no changes in the eyes. On July 28, the parents observed that the child could not see. At this time he was quietly seated at the table, not coughing.

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10. Steffen, in von Ziemssen, H.: Handbuch der speziellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1876, vol. A, pt. 1, p. 278.

11. Sebregondi, quoted by Steffen.[10]

*Cases of Blindness in Pertussis in Literature*

| Author | Date | Sex | Age | Duration of Pertussis Prior to Blindness | Pupils | Eyegrounds | Other Complications | Duration of Blindness | Result | Cause of Blindness |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. Knapp (Arch. Ophth. & Otol. **4**:448, 1874) | 1874 | M | 3 yrs. | 6 wks. | Reaction to light present | Retinal ischemia; disk white | ..... | 3 days | Vision good | Hemorrhagic effusion into sheaths of optic nerve |
| 2. Smith (M. & S. Reporter **49**:17, 1883) | 1883 | F | 5 yrs. | 5 wks. | Dilated, no reaction to light | Normal | Right, then left hemiplegia; unconsciousness; aphasia; dysphagia; spasmodic respirations | 12 days | Vision good | Serous effusion in left cerebral base, later in right cerebral base |
| 3. Callan (Am. J. Cphth. **1**: 219, 1884) | 1884 | F | 11 yrs. | 3 mos. | ? | Papilledema | Mentally disturbed; headaches; pains in joints and limbs | Permanent | Improvement temporary; optic atrophy; vision O. D., movement of hands before face; vision O. S., counts fingers at 8 feet | Passive congestion of brain with edema |
| 4. Silex [da] ..... | 1888 | F | 21 mos. | 3 mos. | No reaction to light | Normal | Morphine poisoning; right hemiplegia; strabismus divergens of left eye | 6 mos. | Vision good; left homonymous hemianopia persisted 3 months | Hemorrhage into the posterior part of internal capsule |
| 5. Alexander (Deutsche med. Wchnschr. **14**: 204, 1888) | 1888 | M | 3 yrs. | 2 mos. | Not dilated; reaction to light present | Normal | Signs of cerebral edema | Permanent | Succumbed to convulsions | Localized edema of occipital portion of brain |
| | | F | 12 yrs. | 2 wks. | No reaction to light | Bilateral optic neuritis; papillae swollen, opaque | ..... | 4 wks. | Still under treatment at time of report; vision constantly improving | Retrobulbar neuritis, or descending encephalomeningitis |
| 6. Jacoby (New York M. J. **53**: 236, 1891) | 1891 | F | 6 yrs. | 3 wks. | Dilated; no reaction to light | Bilateral optic neuritis | ..... | 4 days | Vision normal | Cerebral edema, solely retrobulbar or localized between corpora quadrigemina and occipital lobes |
| | | M | 8 yrs. | 1 mo. | Not dilated; reaction to light present | Normal | Right hemianopia, two days | 6 days | Vision normal | Edema of occipital lobes |
| 7. Gamble (Arch. Ophth. **32**: 359, 1903) | 1903 | F | 8 yrs. | 4 wks. | Dilated; reaction to light present | Blurred disks; optic neuritis | ..... | 6 mos. | Vision normal | Action of toxins of whooping cough on nerve tissue |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 8. Baginsky [64] ..... | 1907 | F | 40 yrs. | 2 wks. | No reaction to light | ? | Convulsions; deafness; idiocy | 9 mos. | Vision normal | Action of toxins of whooping cough on nerve tissue |
| 9. Nacht (Klin. Monatsbl. f. Augenh. **48**: 645, 1910) | 1909 | F | 7 yrs. | 6 wks. | Left, not dilated, no reaction to light; right, reacts sluggishly to light | Papilledema | ..... | 8 wks. | Vision normal | Venous stasis with edema |
| 10. Wiegman (quoted by Hogg: M. J. Australia **1**: 825, 1927) | 1912 | F | 40 yrs. | 4 mos. | ? | Bilateral optic neuritis | ..... | 3 mos. (?) | Normal with moderate constriction of the field in the lower inner quadrant | Action of toxins of whooping cough on nerve tissue |
| 11. Strümpell [17] ..... | 1915 | M | 4½ yrs. | 1 mo. | Dilated, no reaction to light | Papilledema | Ataxia | 2½ wks. | Vision normal | Acute encephalitis or serous meningitis |
| 12. Schmitt (Klin. Wchnschr. **2**: 1413, 1923) | 1923 | F | 2½ yrs. | 15 days | Dilated, reaction to light present | Normal | Unconsciousness; left hemiparesis | 5 wks. | Vision normal | Hemorrhage into occipital lobes in region of calcarine fissure |
| 13. Langer (Jahrb. f. Kinderh. **107**: 57, 1924) | 1924 | F | ? | ? | Dilated, reaction to light present | Normal | ..... | 5 wks. | Vision normal | Circumscribed encephalitis in region of corpora quadrigemina and red nucleus |
| 14. Hogg (M. J. Australia **1**: 825, 1927) | 1927 | M | 16 yrs. | 1 wk. | Not dilated, reaction to light present | Papilledema | ..... | 12 wks. | Vision normal | Action of toxins of whooping cough on nerve tissue |
| 15. Litvak (Am. J. Dis. Child. **36**: 789 [Oct.] 1928) | 1928 | M | 19 mos. | 3 wks. | Dilated unequal, reaction to light present | Normal | Unconsciousness; convulsions; internal strabismus; left facial weakness; weakness of lower extremities; bronchopneumonia | 3 mos. | Vision normal, slight internal strabismus | Encephalitis |
| 16. Hogg (M. J. Australia **2**: 160, 1929) | 1929 | F | 3½ yrs. | 3 mos. | ? | Left disk, optic neuritis, atrophic, pale; right disk, similar, but not as marked | ..... | 6 mos. | Secondary atrophy both disks, vision very limited in right eye | Action of toxins of whooping cough on nerve tissue |
| 17. Eley (New England J. Med. **203**: 162, 1930) | 1930 | F | 19 mos. | ? | ? | Choroiditis; both disks pale | Bilateral internal strabismus; left hemiparesis; paresis right arm | ? | Vision fair | Encephalitis |
| | | M | 2 yrs. | ? | ? | Choroiditis with pale disk (right); left not visualized | Left internal strabismus | ? | Vision almost nil in right eye, nystagmus left eye | Encephalitis |

He complained that the lighted room was dark. An hour later, the attending physician found the patient in a semistuporous condition. The pupils were equal and fixed. A right central facial weakness was observed. A few days later, an ophthalmologist (Dr. M. A. Lasky) found the pupils dilated with no perception of light. The optic disks were choked. Vision in the right eye was 5 diopters; in the left eye, 4 diopters. No hemorrhages or exudates were found.

*Physical Examination.*—On admission to the hospital, examination revealed a well nourished boy who assumed no abnormal posture and lay quietly in bed. The facies was expressionless. The head was normal in size and contour, with no evidence of recent injury. The eyeballs showed slight bilateral protrusion, with edema of the eyelids. The conjunctivae were injected. The pupils were unequal (the left was larger than the right), dilated and fixed. The child was suffering from total loss of sight. The eyegrounds showed a definite papilledema, more marked on the right side, with no hemorrhages or exudates. The vessels were tortuous. A definite right supranuclear facial paresis was noted. The ears and nose presented no abnormalities. The membranes of the mouth were moist. The tongue was coated and deviated toward the right on protrusion. The teeth were in good condition. The pharynx was congested and reflexes were present. Paroxysms of pertussis, with vomiting, were produced by depression of the tongue. There was a hesitancy of speech and some difficulty in pronouncing words. The neck showed no rigidity, enlarged glands or abnormal pulsations. The thorax revealed no bony defects, and the excursion of both sides was equal. The lungs showed numerous moist and crepitant râles. No evidence of bronchial breathing, dulness or other signs of pneumonia were noted. The heart sounds were regular and of good quality, and no murmurs were obtainable. The abdomen was not distended; no masses were felt or tenderness elicited. The liver and spleen were not palpable. The genitalia were normal. There was definite weakness of the right upper and lower extremities. Neurologic findings showed the sensations to be intact. There was no astereognosis or real ataxia. Deep reflexes were present but diminished. Abdominal and cremasteric reflexes were normal. There was no evidence of meningeal irritation. The impression at this time was that we were dealing with multiple small hemorrhages, possible cerebral edema or encephalitis.

*Course.*—During the next four days (August 4 to 8) there was no evidence of improvement; in fact, the disks became more blurred, with increased tortuosity and engorgement of the retinal vessels. At this point, the neurologist's (Dr. I. J. Sands) impression was that the condition was toxic hemorrhagic encephalitis. It was not until August 11 that slight recession in the swelling of the disks was noted. During the next week the right hemiparesis showed a gradual improvement. The speech became more distinct, and the child appeared brighter. The edema of the disks, however, continued to regress very slowly. On August 20, he began to perceive light, and the next day recognized large objects. The right pupil appeared larger than the left, and more sluggish in its response to light. Papilledema was still present, with early signs of optic atrophy. When allowed out of bed, at this time, it was noticed that the child dragged his right leg. The neurologist, on August 23, besides noting the general improvement, commented: "At present, the child is able to recognize some objects, and mention them by name. At times, he shows a definite paraphasia, renaming objects, generally calling them 'chewing gum.'" On August 25, a bilateral catarrhal otitis media

developed. This gradually became worse, and four days later a double myringotomy was performed. At this time the ophthalmologist (Dr. H. H. Waugh) still observed considerable edema of the nerve heads, with optic atrophy. However, the patient was now able to distinguish objects and colors. The facial paresis and weakness of the extremities were greatly diminished.

The child continued to improve slowly. On September 10 examination of the eyes (by Dr. E. M. Beery) showed moderate pallor of the disks, with faintly blurred outlines and scattered areas of retinal atrophy. The next day, the patient was discharged from the hospital. At the time of his release, nystagmoid movements in the horizontal plane were elicited, and the pupils were equal and reacted well to light. The disks, however, still showed bilateral pallor. The speech defect had disappeared, but slight impairment of power in the right upper and lower extremities was noted.

*Subsequent Course.*—The patient was seen at intervals of from ten days to two weeks. The paresis of the right upper extremity disappeared, though a hesitating gait of the right lower extremity remained. On Oct. 15, 1932, the child was reexamined by the ophthalmologist (Dr. M. A. Lasky). He noticed that the nerve heads were flat and pale. No exudate or retinal hemorrhages were seen. Bilateral secondary optic atrophy was still present. Vision in the right eye was 20/70, in the left eye, 20/100.

*Laboratory Data.*—Roentgen studies were made. On August 5, no evidence of a pathologic process was noted in the skull. The sella turcica was normal. The anterior and posterior clinoids were normally formed.

On August 5, the mastoids were of mixed cell pneumatic type and appeared normal.

On August 29, the mastoids were normal; no changes were noted.

Blood studies on August 4 showed: hemoglobin, 78 per cent; red blood cells, 4,940,000; white blood cells, 14,900; polymorphonuclear leukocytes, 37 per cent; small monocytes, 56 per cent; large monocytes, 2 per cent; eosinophils, 2 per cent; Türk's irritation cells, 1 per cent; metamyelocytes, 1 per cent; transitional cells, 1 per cent.

On August 22, examination showed: hemoglobin, 78 per cent; red blood cells, 4,800,000; white blood cells, 14,000; polymorphonuclear leukocytes, 56 per cent; small monocytes, 34 per cent; large monocytes, 4 per cent; eosinophils, 6 per cent.

On August 24, the Wassermann test of the blood was negative.

On August 29, analysis revealed: hemoglobin, 62 per cent; red blood cells, 4,180,000; white blood cells, 11,800; polymorphonuclear leukocytes, 58 per cent; small monocytes, 34 per cent; large monocytes, 4 per cent; eosinophils, 4 per cent.

Studies were made on the spinal fluid on August 4: The pressure was increased; the fluid was clear and contained 2 cells (lymphocytes). Tests showed: albumin, 18 mg.; globulin, negative; sugar, 55 mg. The smear was negative.

*Treatment.*—From August 3 to 7, fluids were restricted; 50 cc. of a 50 per cent dextrose solution was given intravenously daily.

On August 29, myringotomy was done.

## COMMENT

To understand the cause of blindness in whooping cough it is essential to know the usual pathologic changes that may occur in the nervous

system as a result of the disease. The findings and observations of the various authors may be summarized as follows:

1. Hemorrhages into the brain substance.[12]
2. Hemorrhages into the meninges.[13]
3. Functional vascular changes, such as a vasoconstriction with consequent malacia and vasomotor paralysis.[14]
4. Encephalitis due to a virus including hemorrhagic encephalitis.[15]
5. Toxic encephalopathy.[16]
6. Serous meningitis or a disordered cerebral spinal fluid mechanism.[17]
7. Cerebral air embolism.[18]

Moore, Lang, Neame and Doyle[19] were of the opinion that the blindness in infectious diseases was due to a basilar or serous meningitis or to an acute encephalitis which sealed the foramen of Magendie. This caused a distention of the third ventricle which in turn pressed on the optic chiasm. They felt that in cases of temporary amaurosis the sealing of the foramen is of short duration, whereas in permanent blindness this closure continues for a sufficient time to create lasting damage. Rolleston[20] believed that the optic neuritis in these patients was due either to hemorrhages into the sheaths or, probably, to the action of toxins on the optic nerves.

In summarizing the views held by various authors as to the cause of blindness in the twenty charted cases, we find that six were caused by acute encephalitis and five by the action of toxins. Six were due to edema of the retrobulbar or occipital portion of the brain; there was one case of bleeding into the posterior part of the internal capsule, one case of hemorrhagic effusion into the sheaths of the optic nerves, and one case of hemorrhage into the occipital lobe.

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12. Hagenbach, in von Gerhardt, C.: Handbuch der Kinderkrankheiten, Tübingen, H. Laupp, 1877, vol. 2, p. 568; quoted by Rhein.[15g]

13. Canellí: Pediatria **27**:351, 1919. Gazin: Gaz. d. hôp. **54**:292, 1881. Smith: South. M. J. **23**:494 (June) 1930. Capaldo: Policlinico (sez. prat.) **38**:1755, 1931.

14. Hiller, F., and Grinker, R. R.: Functional Circulatory Disturbances and Organic Obstruction of the Cerebral Blood Vessels, Arch. Neurol. & Psychiat. **23**:634 (April) 1930.

15. (*a*) Singer: Ztschr. f. Kreislaufforsch. **20**:338, 1928. (*b*) Vidal: Progrès méd. **1**:270, 1885. (*c*) Blache, quoted by Rhein. (*d*) Simoninis, quoted by Rhein. (*e*) Luce: Deutsche Ztschr. f. Nervenh. **12**:272, 1898. (*f*) West: Brit. M. J. **1**:157, 1889. (*g*) Rhein, J. H. W.: Spastic Diplegia Following Pertussis, J. A. M. A. **44**:697 (March 4) 1905.

16. Husler and Spatz: Ztschr. f. Kinderh. **38**:22, 1924.

17. Strumpell: Deutsche Ztschr. f. Nervenh. **53**:321, 1914-1915.

18. Neubürger: Klin. Wchnschr. **4**:113 (Jan. 15) 1925.

19. Moore, Lang, Neame and Doyle: Brit. J. Ophth. **6**:337 (Aug.) 1922.

20. Rolleston, J. D.: Acute Infectious Diseases, New York, Physicians and Surgeons Book Company, 1925, p. 116.

### COMMENT ON CASE

The presence of hemiplegia, drowsiness and aphasia in the case reported here strongly suggests cerebral involvement. However, the absent pupillary responses are also suggestive of a lesion somewhere outside the cortex. A cortical hemorrhage of a size sufficient to cause the widespread clinical picture observed is inconceivable. The supposed presence of multiple large hemorrhages is also against good judgment. The duration of symptoms and final recession of the papilledema speak against a neoplasm or abscess of the brain, and favor a transient inflammatory condition. Attendant cerebral edema, with or without minute hemorrhages, is frequently found at autopsy in pertussis. This edema, if extensive enough, may interfere with circulation of the cerebrospinal fluid, either by compression of points of egress from the ventricles or by extensive obliteration of the resorbing surface of the brain. A toxic hemorrhagic encephalitis with cerebral edema would explain the clinical findings in this particular case.

### CONCLUSIONS

In reviewing the literature and record of our case of blindness complicating whooping cough, certain definite conclusions present themselves: 1. Amaurosis in pertussis is an exceedingly rare complication and is seldom permanent. 2. The blindness occurs between the first week and the fourth month of the disease and it may last from a few minutes to nine months. 3. The age incidence is widespread and the condition rarely occurs after adolescence. 4. There are no pathognomonic ocular findings. 5. At least 50 per cent of the cases of amaurosis show other cerebral manifestations. 6. In the majority of the cases reviewed, it would appear that the ocular changes are due to cerebral edema or to an acute toxic hemorrhagic encephalitis.

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# FAMILIAL BLEEDING

## REPORT OF TWO CASES

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Werlhof described purpura haemorrhagica in 1735, while Otto,[1] in 1803, in an article called "An Account of an Hemorrhagic Disposition in Certain Families" first recorded a description of hemophilia. Since then many articles have been published to explain the differentiation of and the relationship between these two conditions, as well as to describe many atypical cases of hemorrhagic disease which cannot be grouped with either of these conditions. In 1916 Hess[2] made the statement that "it is becoming increasingly evident that the group termed 'the hemorrhagic diseases' includes a large number of abnormal conditions and that, at the present time, it is a fruitless task to attempt to unravel the various entities embraced by the clinical conditions which are assembled under this general head." This unraveling process has been carried on since and is still progressing.

Hemophilia is easily diagnosed, if the condition seen is in a male and can be traced back through the female. However, true sporadic cases are known to occur, as well as cases in which the defect responsible passes through several generations before it again becomes evident. In addition, the typical case is presented as showing a prolonged clotting time and a normal bleeding time, the latter being determined from a puncture of the skin. There is no diminution in platelets, and retraction of the clot is normal. The prothrombin time is prolonged. No diminution in the blood calcium is usually found, though Hess reported one case with a deficiency in this respect. Hemorrhages into the mucous membranes and joints are common. On the application of a tourniquet no petechial hemorrhages appear.

In purpura haemorrhagica, on the other hand, this production of minute hemorrhages by the use of a tourniquet is held by some observers to be one of the outstanding differential points. In this condition one

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1. Otto, J. C.: An Account of an Hemorrhagic Disposition Existing in Certain Families, M. Reposit. **6**:1, 1803.

2. Hess, A. F.: The Blood and the Blood Vessels in Hemophilia and Other Hemorrhagic Diseases, Arch. Int. Med. **17**:203 (Feb.) 1916.

also finds a typically marked, prolonged bleeding time with normal or only slightly delayed coagulation and prothrombin times. The platelets are usually reduced in number, though Mackay [3] emphasized the fact that reduction does not occur in all cases. The clot is nonretractile. Splenic enlargement is often present. Minor injury is more apt to result in excessive bleeding in this disease than in hemophilia, but hemorrhage into the joints is rarely found.

Glanzman,[4] in 1918, described a group of eight families having a hemorrhagic disease in common, which he differentiated from the foregoing conditions and called hereditary hemorrhagic thrombasthenia. The disease is transmitted as a rule by the female, but occurs in both sexes. The subjects are prone to recurring attacks of epistaxis and are subject to the development of areas of ecchymosis on slight trauma or often none at all. In the cases reported, the platelets were found to be normal or slightly increased. The coagulation time was normal and the bleeding time was not rated as definitely prolonged, although a single puncture wound seemed to produce more blood than would be expected in a normal person. Glanzman particularly called attention to the failure of normal retraction of the clot in his cases.

Ten years later, Giffin [5] reported the case of a woman, aged 33, with a history of frequent epistaxis, which had occurred since the age of 1 year, and severe gastro-intestinal bleeding, which appeared when she reached the age of 20. Her mother, maternal grandmother and maternal great-grandmother also had had frequent epistaxis and profuse menstruation together with excessive bleeding from minor wounds. In this case the coagulation time was normal, but the bleeding and prothrombin times were prolonged. The platelets were increased. No record was made of retraction of the clot.

Shortly thereafter Minot [6] reported five cases from two families with a hemorrhagic condition characterized mainly by prolongation of the bleeding time. He did not attempt to classify it under any of the groups mentioned here and stated that the condition may occur in father and son. It is characterized mainly by recurrent epistaxis and multiple ecchymosis. The abnormality common to all five cases reported was prolongation of the bleeding time. This was noted to be intermit-

3. Mackay, W.: The Blood-Platelet: Its Clinical Significance, Quart. J. Med. **24**:285 (April) 1931.

4. Glanzman, E.: Hereditäre hämorrhagische Thrombasthenie, Jahrb. f. Kinderh. **88**:1 and 113, 1918.

5. Giffin, H. Z.: Unusual Types of Hemorrhagic Disease, Am. J. M. Sc. **175**:44, 1928.

6. Minot, G. R.: A Familial Hemorrhagic Condition Associated with Prolongation of the Bleeding Time, Am. J. M. Sc. **175**:307, 1928.

tently demonstrable and seemed to have a tendency to diminish in severity as the subjects approached adult life. Aside from this, the clotting time was normal, the platelets were normal in number or increased retraction of the clot was normal, and results of the tourniquet test were negative.

Little and Ayres [7] reported the cases of two sisters coming from the fifth generation of a family exhibiting a hemorrhagic diathesis. The dominant feature of both cases was the prolonged bleeding time. The oldest sister had severe menorrhagia, bleeding from the nose and gums and an extensive retinal hemorrhage. Comparison was made between the bleeding time just before a hemorrhage and that after a hemorrhage had been controlled, and no difference was noted. After three months of observation and treatment splenectomy was resorted to, the patient dying nine hours following the operation from intra-abdominal hemorrhage.

Rothman and Nixon [8] reported a case which they classified under the hereditary hemorrhagic thrombasthenias as named by Glanzman. The patient, a boy aged 13, had a history of frequent bruises and purpuric eruptions from birth, as well as recurrent epistaxis beginning at the age of 5 and becoming more frequent. His mother bruised easily and his brother, who died at the age of 3 as the result of an accident, bled freely from minor injuries. The patient's bleeding time was markedly prolonged; the coagulation time was normal. The result of the tourniquet test was negative, and the retraction of the clot was abnormal on one occasion and absent on another.

Recently, Kugelmass [9] included the term hereditary thrombasthenic purpura as one heading in his discussion of hemorrhagic problems. He summarized it as being a familial defect transmitted from generation to generation to both males and females and therefore readily differentiated from hemophilia. The number of platelets fluctuate from low to high values in different members. The bleeding time is prolonged, retraction of the clot retarded and the result of the tourniquet test positive. The spleen is rarely enlarged, and purpuric bleeding is a common symptom.

Attention has been drawn to the discussion of these conditions in the literature by the examination of two brothers with an atypical form of hemorrhagic disease.

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7. Little, W. D., and Ayres, W. W.: Hemorrhagic Disease, J. A. M. A. **91**:1251 (Oct. 27) 1928.

8. Rothman, P. E., and Nixon, N. K.: Familial Purpura Hemorrhagica Without Thrombopenia, J. A. M. A. **93**:15 (July 6) 1929.

9. Kugelmass, I. N.: Management of Hemorrhagic Problems in Infancy and Childhood, J. A. M. A. **99**:895 (Sept. 10) 1932.

REPORT OF CASES

The older boy, I. L., aged 13, was admitted to the hospital in June, 1933, complaining chiefly of pain in the right ankle which had been present for the past three years and had been intermittent. For the past year he had been unable to walk without mechanical assistance. There had been occasional swelling of the joint. The history showed that he had had frequent epistaxis since the age of 18 months, and that a younger brother had a similar condition. Another brother in the family did not exhibit this, and the mother knew of no one on either side of the family with a hemorrhagic tendency. For a few days previous to the patient's admission there had been bleeding from the gums.

Examination revealed hypertrophy of the turbinates with injection of the nasal mucosa on the right side, some oozing from the buccal mucous membranes posteriorly and hypertrophied tonsils which, the boy stated, the family physician was removing by electrocautery. The edge of the spleen was just palpable on deep inspiration. The patient did not bear weight on the right leg, and there was marked atrophy of the muscles of the thigh and leg on that side. No swelling of the ankle or foot was noted. Pressure did not produce pain, though pain was elicited by dorsiflexion. There were many areas of ecchymosis over the lower extremities, together with a few on the upper extremities and back.

On admission, results of urinalysis were negative, as were the tuberculin and Kahn tests. The hemoglobin was 82 per cent, the red blood cell count 5,270,000 and the leukocyte count 12,200, with 77 per cent polymorphonuclears, 1 per cent basophils and 22 per cent lymphocytes. The platelets were estimated as being normal in number on examination of the smear. The bleeding time was seventeen minutes and the clotting time six minutes, estimated by Lee and White's method. The determinations were done repeatedly, and coagulation was found to take place in a persistently short period of time, while the bleeding time varied from sixteen minutes to two and one-half hours. The prothrombin time was nine minutes as was also that of a control. Estimation of the platelets gave a normal result on several occasions. Retraction of the clot was normal. The determination of blood calcium was 10.8 mg. per hundred cubic centimeters. A blood culture was negative. Shortly after admission a spontaneous epistaxis developed during the night, which lasted for several hours but finally responded to applications of ice. Epistaxis occurred two more times during his stay, once requiring packing.

The patient was seen by the orthopedic surgeons, who thought on examination of the right ankle that the condition seemed similar to that found in hemophilia. A roentgenogram revealed evidence of extensive destruction of the articulating surface of the tibia as well as the talus, with partial reduction in the joint space and evidence of minimal productive changes intruding in the talus. These changes agree with the description of those found in the hemorrhages into the joint in hemophilia as described by Birch.[10] Following four weeks of immobilization in a cast with subsequent physical therapy, the symptoms were much improved and motion was reestablished. The boy was discharged, and reported after one month that he had had no more symptoms in the joint and had had only one epistaxis during that time.

The brother, D. L., aged 10, also had had frequent epistaxis on slight trauma or spontaneously since he was 18 months old. The mother sent the additional information that she thought these were becoming less frequent and less severe

10. Birch, C. L.: Hemophilia, J. A. M. A. **99**:1566 (Nov. 5) 1932.

as the boys grew older. This patient also bruised easily and had always had black and blue spots on the extremities. He bled unduly from very slight injuries. He had had no symptoms in the joints and had generally felt well.

Examination revealed a boy of average nutrition. The oral hygiene was poor, and several carious teeth were present. The edge of the liver was questionably felt at the costal margin, but the spleen was not palpable. There were many areas of ecchymosis over the extremities, particularly over the lower ones.

Shortly after he was admitted a spontaneous nasal hemorrhage developed, which lasted for several hours and necessitated packing. Directly after this the bleeding time was more than one hour. The clotting time was thirteen minutes by a modification of the Lee and White method, which was normal as compared to a control. The prothrombin time was eleven minutes, while the clotting time of the control was eight minutes. The blood platelets were definitely increased. The retraction of the clot was normal. The blood calcium was 11.8 mg. per hundred cubic centimeters, and a complete determination of the blood chemistry gave normal readings throughout. Further determinations, done several weeks after the hemorrhage described, gave a definitely prolonged bleeding time and an essentially normal coagulation time. Results of the tourniquet test were negative. Routine examinations of the blood and urine and the Kahn and tuberculin tests gave negative results.

It will be seen that the two cases reported differ definitely from the commoner types of hemorrhagic disease. Even though they tend to be familial, the normal clotting time and markedly prolonged bleeding time exclude hemophilia. They differ from the ordinary picture of purpura haemorrhagica in that the platelets are increased, the retraction of the clot is normal and results of the tourniquet test are negative. They have much in common with those cases which fall in the group of hereditary hemorrhagic thrombasthenias, the differences being that the retraction of the clot is normal and the result of the tourniquet test negative, instead of both being abnormal as usually described in this disease.

Of all the cases mentioned in this paper, the two reported agree closest with those described by Minot [6] and not definitely classified by him. All show a familial tendency, a prolonged bleeding time, normal coagulation time, normal or increased platelets, normal retraction of the clot and a negative result in the tourniquet test. The cases reported here, like his, seem to diminish in severity as the patients grow older.

The mechanism of the production of this prolonged bleeding with the corresponding deficiency present has yet to be explained. It is evident that there are atypical cases of this nature which do not come into the present grouping. Perhaps through description and comparison of these scattered cases the "unraveling" mentioned by Hess will be furthered.

# Progress in Pediatrics

## RENAL GLYCOSURIA IN CHILDHOOD

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When glycosuria is discovered the question immediately arises as to whether one is dealing with benign glycosuria or a pathologic disturbance of the carbohydrate metabolism. The nature of the glycosuria should always be determined, because an incorrect diagnosis may lead to an erroneous prognosis, unnecessary treatment or difficulty in obtaining life insurance. The symptoms and laboratory findings of diabetes mellitus are too well known to bear repetition. However, the group of cases referred to as renal glycosuria demand a more careful consideration, as many patients with this disturbance are often subjected to unwarranted dietetic and insulin therapy and are given an unfavorable prognosis.

### CRITERIA FOR DIAGNOSIS

It has been recognized for some time that renal glycosuria occurs, but many cases so classified in the past do not answer to the present criteria for the diagnosis. The more frequent use of modern laboratory methods has made it possible to maintain a rigid basis for classification. Various classifications of glycosurias have been made. Paullin and Bowcock [1] divided them into three groups: (1) persons with glycosuria having a normal or subnormal blood sugar level after fasting, with normal utilization of dextrose—renal glycosuria and cyclic renal glycosuria or alimentary glycosuria; (2) persons with glycosuria, having a normal blood sugar level after fasting, without the ability readily to mobilize and store increased doses of dextrose—diabetes innocens, and (3) persons with glycosuria having a normal or an increased blood sugar level after fasting and an inability normally to utilize, mobilize and store dextrose— diabetes mellitus. Other classifications have been

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1. Paullin, J. E., and Bowcock, H. M.: M. Clin. North America **12**:1391, 1929.

made by Holst,[2] Malmros,[3] Powelson and Wilder[4] and Graham.[5] Recently Marble[6] arbitrarily chose eight standards in the selection of typical cases of renal glycosuria. These were summarized by him as follows:

1. Glycosuria without hyperglycemia. Sugar should be found in every specimen of urine examined, whether it be voided in the fasting state or after a meal. The amount of sugar excreted per 24 hours is of little importance; it may be large (over 100 Gm.) or small (under 10 Gm.). No fasting blood sugar value (venous) may be 0.12 Gm. per 100 cc. or over and no blood sugar value (venous) after a meal may be 0.17 Gm. per 100 cc. or over.

2. Glycosuria should be largely independent of diet, but may fluctuate somewhat, depending on the amount of carbohydrate ingested.

3. The level of blood sugar should be influenced only slightly by the ingestion of food. The curve obtained after the giving of 100 Gm. of dextrose should be a normal one with no value rising to 0.17 Gm. per 100 cc. or over and with a return to the control value within 2 hours. Often the tolerance curve may exhibit even less than a normal rise.

4. The symptomatology characteristic of diabetes mellitus should be absent.

5. The type of sugar found in the urine should be proved to be dextrose and not levulose, pentose or other substances which reduce alkaline copper solutions.

6. No progression toward true diabetes mellitus should be evident during an arbitrarily chosen period of at least 3 years of observation.

7. For complete study it should be shown that the patient is able to store and utilize carbohydrate in a normal fashion as demonstrated by determinations of the respiratory quotient and metabolism before and after a carbohydrate meal.

8. A common finding, which cannot, however, be regarded as a necessity for diagnosis, is the history of glycosuria occurring in relatives of the patient.

## ETIOLOGY

Many etiologic factors have been proposed as an explanation for the cause of renal glycosuria, but no one factor has been found to be constant in all the reported cases.

*Heredity.*—Because the history of glycosuria in another member of the family is so frequently obtained Hjarne[7] studied heredity as an important factor in influencing carbohydate metabolism. Among 199 persons interrelated by blood, he found 46 with glycosuria. Eighteen had orthoglycemic (renal) glycosuria. Taussig[8] observed nondiabetic

2. Holst, J. E.: Acta med. Scandinav. **63**:47, 1925.

3. Malmros, H.: Acta med. Scandinav. supp. no. 27, 1928.

4. Powelson, H. C., and Wilder, R. M.: Innocent Glycosuria, J. A. M. A. **94**:1562 (May 9) 1931.

5. Graham, George: Quart. J. Med. **16**:236, 1922.

6. Marble, A.: Am. J. M. Sc. **183**:811, 1932.

7. Hjarne, U.: Acta med. Scandinav. **67**:423, 1927.

8. Taussig, A. E.: M. Clin. North America **7**:1545, 1924.

glycosuria in 2 brothers. Bowcock [9] reported a family 18 members of which (representing 58 per cent of the members studied) displayed the presence of a reducing substance in the urine in the absence of other symptoms of diabetes mellitus. Glycosuria was first discovered at 22 months in the youngest and at 78 years in the oldest member. The condition was present in four generations. The response of the blood and urine to the ingestion of dextrose was determined in 5 members; 1 showed the response characteristic of mild diabetes mellitus, 2 of cyclic renal glycosuria and 2 of renal glycosuria. Eight members of this family group were below 14 years of age.

*Renal Disease.*—The question of pathologic change in the kidneys has been considered, but the same opinion is not shared by all investigators. Attention was drawn to the kidney because of phlorhizin glycosuria. Von Mering,[10] in 1886, demonstrated glycosuria following the subcutaneous injection of phlorhizin. Zuntz [11] found that the injection of phlorhizin into the renal artery of a dog resulted in the immediate elimination of sugar from the affected kidney, while the other kidney did not excrete sugar until a definite interval had elapsed and then only in a much smaller quantity. He concluded from this experiment that phlorhizin glycosuria was of purely renal origin. Several authors have noted a nephritic element in their cases of renal glycosuria. Luthje [12] maintained it essential to obtain a history of nephritis in order to establish the diagnosis of renal glycosuria. Lewis and Mosenthal [13] described a case of renal glycosuria in which there were a slightly diminished excretion of phenolsulphonphthalein and a slight elevation of Ambard's coefficient above the normal. Lewis [14] had a patient, an 18 year old Chinese boy, in whom glycosuria appeared while he was under observation for chronic diffuse nephritis. On the other hand, numerous reports deny any renal involvement. Goto,[15] in 1918, stated that the general conception then was that the existence of involvement of the kidneys was not necessary for the occurrence of renal glycosuria. No evidence of nephritis was found in any of the patients described by Marble.[16] The question is still not determined whether a change in the kidneys, not recognized by known laboratory criteria, is primary or the exciting cause when a hereditary predisposition is present.

9. Bowcock, H. M.: Ann. Int. Med. **2**:923, 1929.
10. von Mering, I.: Verhandl. d. Kong. f. inn. Med., 1886, p. 185.
11. Zuntz, N.: Arch. f. Anat. u. Physiol. (Anat. Abt.), 1895, p. 570.
12. Luthje, H.: München. med. Wchnschr. **38**:1471, 1901.
13. Lewis, D. S., and Mosenthal, H. O.: Bull. Johns Hopkins Hosp. **27**:133, 1916.
14. Lewis, D. S.: Renal Glycosuria, Arch. Int. Med. **29**:418 (April) 1922.
15. Goto, K.: Alimentary Renal Glycosuria, Arch. Int. Med. **22**:96 (July) 1918.
16. Marble, A.: Am. J. M. Sc. **183**:827, 1932.

*Trauma.*—Trauma has played a significant rôle in the etiology of several cases of renal glycosuria. Allen and his co-workers [17] reported a case in a man, 42 years of age, who was injured during the World War and remained unconscious for three days. The urine was free from sugar before the injury. The history suggested to the authors that severe trauma was the primary or at least the exciting cause. Strouse and Beifeld [18] described a case of renal glycosuria in which sugar was discovered in the urine about one year after a severe injury to the head. Such clinical observations bring up the question whether intracranial trauma serves as an important etiologic factor or an existing factor when a predisposition to glycosuria already exists.

*Autonomic Imbalance.*—Crawford [19] stated that disturbances of the vegetative nervous system may be the explanation in a certain number of cases. Four of his patients sought advice on account of nervous symptoms which he believed might be attributed to disturbances of the vegetative nervous system. Goldberg [20] concluded from his experiments that renal glycosuria is dependent on disturbances of the vegetative nervous system. Chiari and Fröhlich [21] showed that the excitability of the vegetative nervous system is markedly augmented by diminishing the calcium content of the body. Cammidge and Howard [22] included in their definition of renal glycosuria the statement that the blood shows an absolute and not merely a relative reduction in the proportion of calcium. Hamburger and Brinkman [23] found that the renal threshold for dextrose could be altered by varying the amounts of calcium and potassium in perfusing fluids. Crawford was of the opinion, therefore, that the therapeutic administration of calcium in renal glycosuria may produce a beneficial effect by diminishing the excitability of the vegetative nervous system. Further work seems necessary before any facts are definitely established.

*Endocrine Disturbance.*—Joslin [24] stated that a lowered renal threshold which commonly occurs in both hyperthyroidism and pregnancy

17. Allen, F. M.; Wishart, M. B., and Smith, L. M.: Three Cases of Renal Glycosuria, Arch. Int. Med. **24**:523 (Nov.) 1929.

18. Strouse, S., and Beifeld, A. H.: Case of So-Called "Renal Diabetes," Possibly Traumatic in Origin, J. A. M. A. **62**:1301 (April 25) 1914.

19. Crawford, A. M.: Lancet **2**:214, 1929.

20. Goldberg, N.: Ztschr. f. d. ges. Exper. Med. **59**:468, 1928.

21. Chiari, R., and Fröhlich, A.: Arch. f. exper. Path. u. Pharmakol. **64**:214, 1911.

22. Cammidge, P. J., and Howard, H. A. H.: New Views on Diabetes Mellitus, New York, Oxford University Press, 1923, p. 483.

23. Hamburger, H. J., and Brinkman, R.: Biochem. Ztschr. **88**:97, 1918.

24. Joslin, E. P., in Nelson Loose-Leaf Medicine, New York, Nelson & Sons, 1929, vol. 3, p. 55.

indicates that possibly an endocrine disorder may play a part in renal glycosuria. Conclusive evidence supporting the theory of an endocrine factor is, however, lacking.

### PROGNOSIS

Various opinions are held as to the effect of renal glycosuria on nutrition and its possible transition to diabetes mellitus. Prolonged studies indicate a favorable prognosis. Allan [25] reported a case of renal glycosuria with known constant glycosuria for eighteen years in which no signs or symptoms of diabetes mellitus developed. F. Parkes Weber [26] described a case of renal diabetes in an English woman, 57 years of age, who was known to have passed from 1 to 5 per cent sugar in the urine for at least forty-four years without signs or symptoms of diabetes mellitus. There was no evidence that the persistent glycosuria had an injurious influence on her general health. Crawford [19] stated that renal glycosuria has been known to persist for many years without apparent deterioration in health, and that so far as the present knowledge goes, there is no known relationship between renal glycosuria and diabetes mellitus. According to Joslin,[24] the condition in itself seems to have no ill effects on renal function. Although renal glycosuria probably does not change the diabetes, he usually gives a guarded prognosis because of the possibility of an error in classification or the possibility of coincidental renal glycosuria and diabetes mellitus, as reported by Curran and Mills.[27] Young,[28] on the other hand, stated that renal glycosuria, because of its chronicity, may so undermine nutrition that proper development does not occur. He believed that all cases of renal glycosuria should be considered as at least potential cases of diabetes mellitus. The majority of investigators, however, give a more favorable prognosis, and consider renal glycosuria benign.

### TREATMENT

Until the etiologic factors are more certainly established treatment must be on an empirical basis. Goto [15] stated that there is no assurance that it is harmless to give persons with renal glycosuria carbohydrate and dextrose in large amounts. The normal threshold for dextrose may be further depressed on such a regimen. Young [28] advocated the frequent feeding of small amounts of carbohydrates in order to prevent blood sugar values above the lowered renal threshold in cases of renal glycosuria. A high protein content is also maintained in this diet.

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25. Allan, W.: A Case of Renal Glycosuria, J. A. M. A. **80**:471 (Feb. 17) 1923.
26. Weber, F. Parkes: Lancet **2**:71, 1931.
27. Curran, J. A., and Mills, C. A.: J. Lab. & Clin. Med. **13**:646, 1928.
28. Young, J. G.: Texas State J. Med. **25**:478, 1929.

However, neither Goto nor Young was able to support their hypothesis that an unlimited carbohydrate intake depresses the patient's tolerance for carbohydrates. Crawford [19] referred to a case in which calcium lactate and parathyroid extract were given, and a temporary reduction in the glycosuria was produced. Lewis and Mosenthal [13] gave calcium chloride by mouth for three days, but it had no effect in reducing the output of sugar. In view of the benign course of renal glycosuria in cases carefully observed over a long period of time the rationale of dietetic management can be questioned. The specific value of calcium therapy cannot be evaluated until unequivocal evidence of its action in controlling glycosuria is presented.

### OCCURRENCE IN CHILDREN

Cases in children are mentioned in the literature, but few of them are fully described. Findley and Rabinowitch,[29] in summarizing previous cases, found 1 patient of 6 years and 5 of less than 10 years. Lemann [30] observed a boy from the age of 3 years and 4 months until 6 years of age. During that period the child had constant glycosuria without hyperglycemia irrespective of diet. The patient showed no symptoms of diabetes mellitus, and his weight increased from 33 to 42 pounds (15 to 19 Kg.). Paullin and Bowcock [1] described the condition in a poorly nourished and ill-developed white girl who was unable to walk because of muscular weakness of her lower extremities. No mental impairment was present. Sugar was first noted in the urine at 2 years of age, and during a period of three years there were no symptoms of diabetes mellitus. Eight units of insulin a day did not appreciably lower the amount of sugar excreted in the urine, and even the production of insulin shock did not rid the urine of sugar. It was the authors' opinion that the constant loss of dextrose in the urine might have influenced the retarded physical development. Young's [28] patient was a girl 8 years of age in whom glycosuria was found at the age of 3 years. Insulin was given, with the production each time of a hypoglycemic reaction. On a restricted diet the urine continued to show glycosuria, and the child did not gain weight or grow normally. The institution of a diet low in carbohydrates with frequent feedings resulted in a normal gain in weight and development. At the time of the report she had attained normal weight and the urine was free from sugar most of the time. Goldbloom [31] reported a case in a 20 month old infant whose father also had renal glycosuria. The infant was observed for only six weeks, and the glycosuria disappeared. No subsequent data

29. Findley, F. G., and Rabinowitch, I. M.: Quart. J. Med. **17**:260, 1923.
30. Lemann, I.: Southern M. J. **16**:592, 1923.
31. Goldbloom, A.: Canad. M. A. J. **14**:950, 1924.

were available so that it is not certain whether this is a true case of renal glycosuria.

Other cases of renal glycosuria in children appear in the literature, but those cited in this discussion merely serve to emphasize the fact that the condition is a clinical entity in childhood and may be recognized at this period of life. This brings up the question of whether those cases which have been recognized in adult life ever presented symptoms sufficiently characteristic to have established the diagnosis during childhood. After going over the cases on record the question must be left open, as the information available is not conclusive enough to decide the question. The case reported by Bailey [32] is, however, interesting from this standpoint. He reported a case in a woman, aged 31, who had been in poor health from early infancy. She was always poorly nourished, and her mother told her that when she was a child her urine was irritating. Meticulous care and hygiene were necessary to prevent irritation of the vulva. Bailey was of the opinion that the history pointed strongly to this being a congenital condition.

## REPORT OF A CASE

The following case brings up some interesting points with regard to renal glycosuria in children:

*History.*—V. K. was admitted to the Research and Educational Hospital on July 18, 1932, at the age of 5 years and 4 months, for a metabolic study because of glycosuria. This was discovered accidentally when the urine was examined during the course of an infection of the upper respiratory tract to rule out pyelitis. Two and a half weeks preceding the infection of the upper respiratory tract she was in contact with a child in whom scarlet fever developed two days later. On June 23 she had tonsillitis, nasal discharge, a nonproductive cough and fever. These symptoms lasted for three days but she remained in bed five days. During the course of the febrile period an examination of the urine revealed sugar. At the onset of the illness sugar was found in the urine in association with acetone, but no casts or red blood cells were noted. The patient was placed on a restricted carbohydrate diet by her physician, but the glycosuria continued. The patient's father, a dentist, examined the urine daily, and constantly found a reduction with Haine's solution until the day of admission. No examination of the urine had ever been made before the febrile period of June 1932. In spite of exposure to a child with scarlet fever there was no evidence that our patient had the disease in a manifest or an atypical form or any of the complications (nephritis). At no time was there clinical evidence for the diagnosis of diabetes mellitus. A physician who had her under his care since early infancy stated that she never showed evidence of disturbed carbohydrate metabolism nor had she ever had symptoms suggesting nephritis. On entrance to the hospital symptoms of occasional dizziness and a "tired feeling" in her back for several days preceding admission were the only complaints elicited.

32. Bailey, C. V.: Am. J. M. Sc. **157**:221, 1919.

Past illnesses included occasional respiratory infections of the upper tract and pertussis at 3 years of age. At 4 years she received diphtheria toxin-antitoxin with no complications.

The patient was the only child born at full term, and weighed 8½ pounds (3,856 Gm.). Labor lasted for eighteen hours, and forceps were used with ether anesthesia. Except for a slight bruise of the right upper eyelid there was no evidence of cerebral trauma at birth and the history following birth corroborates the statement. Her mental and physical development were normal.

The family history was of considerable interest. The child's maternal grandfather had diabetes mellitus which was discovered twelve years before. The disease was apparently mild, for the treatment consisted of a restricted carbohydrate diet only. When the grandfather's condition was diagnosed as diabetic the patient's mother was examined. A single specimen of urine contained sugar. However, the urine was normal six years later during routine prenatal examination of the urine. Two days before bringing the patient to the hospital, while she was excited,

TABLE 1.—*Sugar Tolerance Curve on Two Different Occasions*

| Time | | Blood Sugar (Venous), Mg. | Sugar in Urine | Acetone in Urine | Volume of Urine, Cc. | Specific Gravity | Total Gm. Sugar in Urine |
|---|---|---|---|---|---|---|---|
| 7/25/32: 31.2 Gm. Dextrose with 350 Cc. Water | | | | | | | |
| 8:30 | Fasting..... | 63 | | | | | |
| 9:30 | First hour..... | 170 | + | 0 | 75 | | |
| 10:30 | Second hour..... | 143 | + | 0 | 270 | | |
| 11:30 | Third hour..... | 70 | + | 0 | 35 | | |
| | | | | | | | 2.6 |
| 6/1/33: 36.2 Gm. Dextrose with 300 Cc. Water | | | | | | | |
| 8:30 | Fasting..... | 75 | + with 1 drop | 0 | 135 | 1.024 | 2.24 |
| 8:35 | Dextrose taken | | | | | | |
| 9:35 | First hour..... | 158 | + with 1 drop | 0 | 100 | 1.015 | 2.11 |
| 10:40 | Second hour..... | 91 | + with 1 drop | 0 | 10:55, 110 | 1.006 | 1.2 |
| 11:35 | Third hour..... | 94 | + with 1 drop | 0 | 25 | 1.012 | 0.5 |

a reduction was obtained, but sugar was not present on the following day. The information was also offered that a physician found sugar in the urine of a maternal uncle, and that the glycosuria was not due to diabetes mellitus.

*Physical Examination.*—The patient was a well nourished and well developed white child, 5 years and 4 months of age, with no objective evidence of ill health. She was 111.75 cm. in height and weighed 18.9 Kg. Physical examination revealed a normal condition except for small cryptic tonsils, pharyngitis and an old traumatic scar on her right upper eyelid due to delivery with forceps.

After being studied for two months in the ward, during which time a tonsillectomy was performed under ether anesthesia, her weight was 17.7 Kg. The pharyngitis continued during the early period of hospitalization. Bacteriologic study of the pharyngeal flora revealed hemolytic staphylococci. Roentgenograms of the sinuses gave negative results. The blood pressure during the first week of observation was 110 systolic and 90 diastolic and 122 systolic and 84 diastolic, but later it became 86 systolic and 54 diastolic. The clinical course during the period of hospitalization was entirely uneventful and afebrile.

*Laboratory Findings.*—Type of Urinary Sugar: Dextrosozone crystals were identified with the phenylhydrazine test. A reduction was obtained with Benedict's

TABLE 2.—*Effect of Quantitative Diets on Glycosuria*

| Diet | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period, Days | Calories | Protein, Gm. | Fat, Gm. | Carbohydrate, Gm. | Dextrose | Fatty Acid | Daily Intake of Dextrose, Gm. | Activity | Glycosuria | Daily 24 Hour Excretion of Urine, Gm. | Basal Metabolic Rate | Blood Sugar Values After Fasting (Folin-Wu), Mg. per 100 Cc. |
| 22 | 1,160 | 40 | 80 | 70 | 101.2 | 90.4 | 64.8 to 101.2 | Ward | Constant except one specimen, midnight to 7 a.m.; sugar present remainder of the day | 0.22 to 5.02 | +31<br>+23 | 85<br>63<br>74 |
| 11 | 1,155 | 40 | 55 | 125 | 153.4 | 67.0 | 141 to 153.4 | Ward | Constant | 2.47 to 8.07 | + 8<br>+12 | |
| 17 | 1,155 | 40 | 35 | 170 | 196.7 | 49.9 | 196.7 | Ward | Constant | 0.7 to 10.24 | +30<br>+11<br>+16.6 | 78<br>80<br>87<br>61<br>75 |
| 9 | Mixed diet of the ward..... | | | | | | | Ward | Constant | 1.32 to 12.58 | | |

TABLE 3.—*Synchronous Determinations of Sugar in the Urine and Blood*

Diet: 1,155 Calories; Protein, 40; Fat, 35; Carbohydrate, 170

| | 9/1/32 | | 9/2/32 | | 9/3/32 | |
|---|---|---|---|---|---|---|
| Time | Blood | Urine | Blood | Urine | Blood | Urine |
| 2 a. m. ..... | .. | .. | 87 | + | 61 | + |
| 6 a. m. ..... | .. | .. | .. | + | .. | + |
| 7 a. m. ..... | .. | .. | .. | .. | 75 | |
| 7:30 a. m., meal | | | | | | |
| 8 a. m. ..... | .. | + | .. | + | .. | + |
| 9:30 a. m. ..... | 67 | .. | 91 | | | |
| 10 a. m. ..... | .. | + | .. | + | .. | + |
| 11 a. m., meal | | | | | | |
| 12 noon..... | .. | + | .. | + | | |
| 1 p. m. ..... | 95 | .. | 73 | | | |
| 2 p. m. ..... | .. | + | .. | + | | |
| 4 p. m., meal | | | | | | |
| 4 p. m. ..... | .. | + | .. | + | | |
| 6 p. m. ..... | 102 | + | 82 | + | | |
| 8 p. m. ..... | .. | + | .. | + | | |
| 10 p. m. ..... | 87 | + | 71 | + | | |

| 24 Hour Test of Urine (from 7 a. m. to 7 a. m.) | Urine, Cc. | Sugar, Gm. |
|---|---|---|
| Sept. 1 to Sept. 2..... | 770 | 5.55 |
| Sept. 2 to Sept. 3..... | 760 | 5.33 |
| Sept. 3 to Sept. 4..... | 770 | 10.24 |

solution before fermentation of the urine with yeast, but not afterward. Bial's test for fructose was negative when compared with controls. The necessity of differentiating the type of urinary sugar is illustrated by the reports of Marble[16] and Neuman,[33] who observed several cases of chronic essential pentosuria in childhood which clinically resembled renal glycosia.

Carbohydrate Tolerance Curve: The carbohydrate tolerance was determined after giving orally 1.75 Gm. of dextrose in water per kilogram of body weight

33. Neuman, L.: M. Ann. District Columbia **1**:79, 1932.

(from 9 to 12 per cent). The blood sugar value rose to 170 at the end of one hour, and did not return to normal until three hours after the dextrose was given (table 1). The second test was made ten months later, and showed an earlier return to normal values.

Effect of Diet: An increase in the daily intake of dextrose from 101.2 to 196.7 Gm. influenced the output of sugar only slightly. No change was noted in the blood sugar values when the intake of dextrose was increased (table 2). Glycosuria was constantly present except in one specimen from midnight to 7 a. m. after fasting, but glycosuria was present the remainder of the day.

Synchronous Examination of the Blood and Urine: Frequent determinations of the blood sugar values and examination of the urine were made for forty-eight

TABLE 4.—*Effect of Insulin on Urine and Blood Sugar*

Diet: 1,155 Calories; Protein, 40; Fat, 35; Carbohydrate, 170

| | 9/6/32 | 9/7/32 | 9/8/32 | | 9/9/32 |
|---|---|---|---|---|---|
| | Insulin: 3 Units, 20 Minutes Before Meals Three Times a Day | Insulin: 3 Units, 20 Minutes Before Meals Three Times a Day | Insulin: 5 Units, 20 Minutes Before Meals Three Times a Day | | Insulin: 5 Units, 20 Minutes Before Meals Three Times a Day |
| Time | Glycosuria | Glycosuria | Glycosuria | Blood Sugar | Glycosuria |
| 2 a. m. | .. | + | + | .. | + |
| 4 a. m. | .. | + | | | |
| 6 a. m. | .. | + | + | .. | + |
| 7 a. m. | | | | | |
| 8 a. m. | + | .. | .. | .. | + |
| 9:40 a. m. | .. | .. | .. | 80 | |
| 10 a. m. | + | + | + | | |
| 11 a. m. | | | | | |
| 12 noon | + | + | + | .. | + |
| 1 p. m. | .. | .. | .. | 68 | |
| 2 p. m. | + | + | .. | .. | + |
| 4 p. m. | | | | | |
| 4 p. m. | + | + | + | | |
| 6 p. m. | + | + | + | 63 | + |
| 8 p. m. | .. | + | + | .. | + |
| 10 p. m. | + | + | + | .. | + |
| 12 midnight | + | + | .. | .. | + |

| 24 Hour Test of Urine (from 7 a. m. to 7 a. m.) | Urine, Cc. | Sugar, Gm. |
|---|---|---|
| Sept. 6 to Sept. 7 | 355 | 1.89 |
| Sept. 7 to Sept. 8 | 600 | 5.09 |
| Sept. 8 to Sept. 9 | 453 | 2.43 |
| Sept. 9 to Sept. 10 | 710 | 2.95 |

hours to determine synchronous values and to obtain repeated analysis two hours after meals (table 3). Glycosuria was constantly present and all blood sugar values were normal. Six synchronous examinations of the blood and urine revealed glycosuria without hyperglycemia. Blood sugar values two hours after meals were normal.

Effect of Insulin: The effect of insulin on glycosuria and blood sugar values was studied for four days. Three units of insulin was given twenty minutes before meals for two days and 5 units for the following two days. The total amount of sugar excreted was only slightly reduced. Blood sugar values two hours after meals were slightly lower than when no insulin was given. Insulin shock was not produced. Glycosuria was constant in spite of 9 units given daily for two days and 15 units daily for two days (table 4).

Renal Function: The phenolsulphonphthalein, Mosenthal and concentration and dilution tests showed normal reactions. The nonprotein nitrogen of the blood was

34 mg. in July 1932 and 25 mg. in June 1933. The examination of the urine on June 1, 1933, gave normal results except for a positive Benedict reaction and the presence of occasional white blood cells.

After admission casts were occasionally found in the urine for one week, and acetone for three weeks. However, tests for diacetic acid were negative, and red blood cells were not seen. During this period she was afebrile but had slight pharyngitis. Following an anesthetic for a tonsillectomy there was transient ketonuria.

*Course.*—The patient was readmitted to the Research and Educational Hospital on June 1, 1933, for further studies. Additional information was furnished by the parents at this time. They noted a gain in weight and an increase in height. At no time had she complained of polydypsia, polyphagia or polyuria. She urinated from four to five time a day, and had no nocturia. Her bowels moved daily. She did not complain of headache, dizziness, spots before her eyes or lumbar pain. At no time was there general or localized edema.

Her urine had been tested for sugar with Haine's solution from once to three times a week since she was discharged from the hospital on Sept. 18, 1932. On no occasion had the test been negative. The mother recalled at this visit that since about 4 years of age the patient frequently complained that her "body hurt," referring to the vulva. She never complained of itching or burning. Whenever the child complained the mother found the vulva reddened. This was noted several times a month; cold cream applied to the vulva gave immediate relief.

The child had been well except for two infections. During December 1932 she had an infection of the upper respiratory tract with a temperature as high as 103 F. rectally for three days. Recovery was uneventful. No acetone odor to the breath or drowsiness was noted during the febrile period. Following this the patient remained well until May 5, 1933, when she had a typical case of measles. The eruption lasted for one week. There were no complications. Her temperature rose to 104 F. by mouth on the day the eruption developed and became normal on the fourth day. During or following neither of the infections was there any evidence of ketosis or of diabetes mellitus.

On readmission the blood calcium was 11 mg. and the potassium 19.8 mg. The Kahn reaction of the blood and Pirquet test were negative. Cytologic observations of the blood were normal.

Bacteriologic examination of the vulvovaginal flora on June 14 revealed a Mycoderma strain of yeast which has normally been found on the skin.

A physical examination on June 16, 1933, at which time she was 6 years and 2 months of age, revealed a normal child except for a slight redness of the vulva. She had gained 1.8 Kg. and had grown 5.25 cm. since her first admission. The blood pressure was 98 systolic and 68 diastolic. Laboratory examinations revealed glycosuria without hyperglycemia. The sugar tolerance curve was normal.

## COMMENT

The patient presented constant glycosuria without hyperglycemia for over a year. During this period there was no evidence of transition to diabetes mellitus. In fact, the sugar tolerance curve was more representative of renal glycosuria at the end of one year's observation than when she was first studied. The first sugar tolerance curve was suggestive of mild diabetes mellitus, but subsequent observations indicated normal blood sugar values after the ingestion of carbohydrates.

Her nutrition has remained in a good state, and at no time has she complained of the symptoms characteristic of diabetes mellitus. She withstood a general anesthetic, an infection of the upper respiratory tract and an attack of measles—conditions which would be expected to aggravate diabetes mellitus, without symptoms to suggest the inability to metabolize carbohydrates normally.

The onset of the glycosuria could not be ascertained. The history, however, of vulvovaginitis suggests its beginning before the respiratory infection of June 1932. Hesseltine [34] showed that glycosuria supplies a favorable medium for vulval mycosis which may have accounted for the symptom, although no fungi were found in June 1933.

On the other hand, it is possible that the infection in June 1932 precipitated a change in the renal threshold for dextrose, as a hereditary predisposition already existed. Although there were no clinical findings or reactions to laboratory tests to indicate impaired renal functions casts were found in the urine, and the blood pressure was somewhat elevated when the patient was first studied.

The patient was a calm child, normally proportioned, and had no symptoms or signs to suggest a disturbance of the vegetative nervous system or endocrine system. No one cause discussed under etiology can be definitely assigned as the cause of glycosuria.

## SUMMARY

The subject of renal glycosuria is reviewed, and special reference is made to its occurrence in childhood. The criteria for diagnosis and etiology are considered in detail. In the case reported all the recent diagnostic criteria were fulfilled except the duration of the glycosuria. A benign course was observed for a period of over one year in spite of an unlimited intake of carbohydrate.

NOTE.—Since this communication was submitted for publication glycosuria has been constantly present in spite of the patient's excellent general health and normal growth and development.

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34. Hesseltine, H. C.: Diabetic or Mycetic Vulvovaginitis, J. A. M. A. **100:** 177 (Jan. 21) 1933.

# Pediatric Biographies

## JOHN CONRAD OTTO
1774-1844

### A NOTE ON THE HISTORY OF HEMOPHILIA

JOHN RUHRÄH, M.D.
BALTIMORE

John Conrad Otto (1774 to 1844) was born in Woolbridge, N. J. He studied at Princeton, where he received the degree of A.B. in 1792, and then entered the office of Benjamin Rush; he obtained his degree in medicine from the University of Pennsylvania in 1796. He contracted yellow fever in the epidemic of 1798, and the same year became a physician for the Philadelphia Dispensary. When Rush died in 1813, Otto was appointed one of the physicians for the Pennsylvania Hospital, a position which he held for twenty-two years. He was a fellow of the College of Physicians, and from 1840 until his death on June 26, 1844, was vice president of that organization.

His account of hemophilia, so named by Schönlein, was published in the *Medical Repository* in 1803, and was based on a study of a family named Smith, from the neighborhood of Plymouth, N. H. In 1805, in Coxes' *Medical Museum,* he had another article about the disease in the family of Benjamin Benney, of Maryland, which he had mentioned in his first article.

*An Account of an* HEMORRHAGIC DISPOSITION *existing in certain Families. By* JOHN C. OTTO, *M. D. of Philadelphia.*

ABOUT seventy or eighty years ago, a woman by the name of Smith, settled in the vicinity of Plymouth, New-Hampshire, and transmitted the following idiosyncrasy to her descendants. It is one, she observed, to which her family is unfortunately subject, and had been the source not only of great solicitude, but frequently the cause of death. If the least scratch is made on the skin of some of them, as mortal a hemorrhagy will eventually ensue as if the largest wound is inflicted. The divided parts, in some instances, have had the appearance of uniting, and have shown a kind disposition to heal; and, in others, cicatrization has almost been perfect, when, generally about a week from the injury, an hemorrhagy takes place from the whole surface of the wound, and continues several days, and is then succeeded by effusions of serous fluid; the strength and spirits of the person become rapidly prostrate; the countenance assumes a pale and ghastly appearance; the pulse loses its force, and is increased in frequency; and death, from mere debility, then soon closes the scene. Dr. Rogers attended a lad, who had a slight cut on his

foot, whose pulse "was full and frequent" in the commencement of the complaint, whose blood "seemed to be in a high state of efferverscence." So assured are the members of this family of the terrible consequences of the least wound, that they will not suffer themselves to be bled on any consideration, having lost a relation by not being able to stop the discharge occasioned by this operation.

## MEDICAL REPOSITORY.

VOL. VI.—No. I.

### ARTICLE I.

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ABOUT seventy or eighty years ago, a woman by the name of Smith, settled in the vicinity of Plymouth, New-Hampshire, and transmitted the following idiosyncrasy to her descendants. It is one, she observed, to which her family is unfortunately subject, and had been the source not only of great solicitude, but frequently the cause of death. If the least scratch is made on the skin of some of them, as mortal a hemorrhagy will eventually ensue as if the largest wound is inflicted. The divided parts, in some instances, have had the appearance of uniting, and have shown a kind disposition to heal; and, in others, cicatrization has almost been perfect, when, generally about a week from the injury, an hemorrhagy takes place from the whole surface of the wound, and continues several days, and is then succeeded by effusions of serous fluid; the strength and spirits of the person become rapidly prostrate; the countenance assumes a pale and ghastly appearance; the pulse loses its force, and is increased in frequency; and death, from mere debility, then soon closes the scene. Dr. Rogers attended a lad, who had a slight cut on his foot, whose pulse "was full and frequent" in the commencement of the complaint, and whose blood "seemed to be in a high state of efferverscence." So assured are the members of this family of the terrible consequences of the least wound, that they will not suffer themselves to be bled on any consideration, having lost a relation by not being able to stop the discharge occasioned by this operation.

Various remedies have been employed to restrain the hemorrhagies—the bark, astringents used topically and internally,



The first page of Otto's article in the Medical Repository.

Various remedies have been employed to restrain the hemorrhagies—the bark, astringents used topically and internally, strong styptics, opiates, and, in fact, all those means that experience has found serviceable, have been tried in vain. Physicians of acknowledged merit have been consulted, but have not been able to direct any thing of utility. Those families that are subject to certain complaints are occasionally relieved by medicines that are inefficacious when applied to others; and family receipts are often of greater advantage in restoring them, than all the

drugs the materia medica offers for that purpose. A few years since the sulphate of soda was accidentally found to be completely curative of the hemorrhages I have described. An ordinary purging dose, administered two or three days in succession, generally stops them; and, by a more frequent repetition, is certain of producing this effect. The cases in which the most powerful, and apparently most appropriate remedies have been used in vain, and those in which this mode of treatment has been attended with success, are so numerous, that no doubt can exist of the efficacy of this prescription. The persons who are subject to this hemorrhagic idiosyncrasy, speak of it with the greatest confidence. Deceptions may take place from accidental coincidence; but when a complaint has often occurred, and been almost uniformly fatal without the administration of a certain medicine, and has constantly yielded when it has been given, scepticism should be silent with regard to its utility. Nor should our inability to account for the fact, upon the theory and principles we have adopted, be conceived a sufficient reason for disbelieving it. An attempt to explain the mode of operation of this valuable remedy might give birth to much speculation. As the affection has been attended with mortality, and there is generally a disposition to give relief as early as possible, experiments have not been made with the other neutral salts to learn their comparative effect; nor have medicines been tried whose operation might be supposed to be similar. The prescription being known to the whole family, application is rarely made to a physician, and when it is, it is rather with a view of directing him how to proceed, than of permitting him to make a series of trials and observations which might be at the hazard of the life of the patient. The utility of the sulphate of soda cannot arise from its debilitating effects, since it has been found serviceable when the previous depletion has been great, the strength much exhausted, and the system has evidenced symptoms of direct debility. Perhaps time will elucidate its mode of operation, and some general principles may be developed that may be applied to advantage in restraining ordinary hemorrhages; but reasoning upon what has been discovered to be useful in idiosyncrasies, and applying it to the general constitution of human nature, must necessarily be vague and productive of occasional evil. In every case, however, a doubtful remedy is preferable to leaving the patient to his fate. The sulphate of soda has constantly succeeded when administered; but the prescription being in the possession of the Shepard family, the descendants of Smith, and the cases that have been attended by physicians not being very numerous, it is impossible to ascertain the various states of the system in which it has been given, or to form any correct conclusions respecting its manner of acting. No experiments have been made on the blood to discover if any or what changes take place in it.

It is a surprising circumstance that the males only are subject to this strange affection, and that all of them are not liable to it. Some persons, who are curious, suppose they can distinguish the bleeders (for this is the name given to them) even in infancy; but as yet the characteristic marks are not ascertained sufficiently definite. Although the females are exempt, they are still capable of transmitting it to their male children, as is evidenced by its introduction and other instances, an account of which I have received from the Hon. Judge Livermore, who was polite enough to communicate to me many particulars upon this subject. This fact is confirmed by Drs. Rogers and Porter, gentlemen of character residing in the neighbourhood, to whom I am indebted for some information upon this curious disposition. When the cases shall become more numerous, it may perhaps be found that the female sex is not entirely exempt, but, as far as my knowledge extends, there has not been an instance of their being attacked.

The persons subject to this hemorrhagic disposition are remarkably healthy, and, when indisposed, they do not differ in their complaints, except in this particular, from their neighbours. No age is exempt, nor does any one appear to be particularly liable to it. The situation of their residence is not favourable to scorbutic affections or disease in general. They live, like the inhabitants of the country, upon solid and nutritious food, and when arrived to manhood, are athletic, of florid complexion, and extremely irascible.

Dr. Rush has informed me, he has been consulted twice in the course of his practice upon this disease. The first time, by a family in York, and the second, by one in Northampton county, in this state. He likewise favoured me with the following account, which he received some years since from Mr. Boardley, of a family in Maryland, afflicted with this idiosyncrasy.

"A. B. of the State of Maryland, has had six children, four of whom have died of a loss of blood from the most trifling scratches or bruises. A small pebble fell on the nail of a forefinger of the last of them, when at play, being a year or two old: in a short time, the blood issued from the end of that finger, until he bled to death. The physicians could not stop the bleeding. Two of the brothers still living are going in the same way: they bleed greatly upon the slightest scratch, and the father looks every day for an accident that will destroy them. Their surviving sister shows not the least disposition to that threatening disorder, although scratched and wounded. The father gave me this account two days since, but I was not inquisitive enough for particulars."

# Pediatrics in Art

## THE INFANT'S CHAIR

JOHN RUHRÄH, M.D.
BALTIMORE

Anton Raphael Mengs (1728 to 1779), who is said to have been more learned than inspired, left a number of pictures, at least one of which has a pediatric interest. This hangs in the Prado in Madrid and is a portrait of two children, evidently of the nobility. It illustrates

Portrait of two infants by Mengs.

fairly well what the very rich provided in the way of show clothes for their children. The baby with a teething ring in its hand sits in a fine little arm chair with a restraining board, which, for purposes of the artist, has been put on a stand. The head is covered with a cap not unlike those seen today. The older child is dressed in a long gown of stiff satin and fingers a jeweled order. The cap is tied snugly about the head. The children of the very rich were as handicapped in those days as they are today.

# News and Comment

## UNIVERSITY NEWS

Prof. Albrecht Peiper of the University Children's Clinic of the Charité, Berlin, has been named director of the Children's Hospital of Barmen.

Dr. Herman Zischinsky has been named director of the Infectious Pavilion of the Wilhelminen Hospital in Vienna to replace Dr. Pospischill, deceased.

Dr. Oscar M. Schloss has resumed private practice on his resignation as professor of pediatrics at the Cornell University Medical School and as pediatrician-in-chief of the New York Hospital. He is to remain with the medical school as professor of clinical pediatrics and with the hospital as attending pediatrician. He also will continue his research work at the hospital. Dr. Samuel Z. Levine, now associate professor and attending pediatrician, has been appointed acting pediatrician-in-chief and acting professor of pediatrics.

## SOCIETY NEWS

**American Pediatric Society.**—At the meeting of the society at Asheville, N. C., from May 3 to 5, the following officers were elected: president, Dr. Borden S. Veeder; vice president, Dr. Henry J. Gerstenberger; secretary-treasurer, Dr. Hugh McCulloch; recorder and editor, Dr. C. A. Aldrich; member of the council, Dr. James L. Gamble. At the same meeting Dr. Allen M. Butler of Boston and Dr. John Lyttle of New York were elected to membership.

## DEATHS

Dr. Charles B. Boidt, chief of the laboratory at the Hôpital des Enfants-Malades, died recently in Paris.

# Abstracts from Current Literature

## Pathology, Bacteriology and Biochemistry

Effect of Experimental Massive Hemorrhages on the Size of the Red Blood Cell in Dogs. A. R. Camero and E. B. Krumbharr, Am. J. Physiol. **103**:407 (Feb.) 1933.

Massive hemorrhages in dogs produced a marked increase in the scatter of the erythrocyte diameter and an increase in the average cell diameter.

Nourse, Cleveland.

The Effect of a High Vegetable Protein Diet on the Trichomonad Flagellates of Rats. Robert Hegner, Am. J. Trop. Med. **13**:535 (Sept.) 1933.

The author carried out an experiment to determine the effect of a diet high in vegetable protein on Trichomonas in rats. He used three groups of albino rats highly infected with intestinal Trichomonas. To one group he fed a normal diet. The other groups received a diet high in animal protein and a diet high in vegetable protein, respectively. He found that vegetable protein was almost as effective as animal protein in rendering the intestine of the rat host unfavorable for Trichomonas.

Burpee, Augusta, Ga.

Recovery from Experimental Barbital Poisoning Under Various Types of Fluid Administration. W. E. Gower and J. Van De Erve, J. Pharmacol. & Exper. Therap. **48**:141 (June) 1933.

Diuresis hastened the recovery of dogs with barbital poisoning. By vein, saline solutions were more effective than dextrose solutions, probably because of the dehydrating action of the latter. Saline solution by mouth caused variable diuresis, but when diuresis was maintained this route was most effective. Hypodermoclysis was not effective, because absorption was too slow.

Pilcher, Cleveland.

Studies on Calcium: VIII. Therapeutic Effects of Calglocon (Calcium Gluconate) on Thrombophlebitis Edema. Arnold L. Lieberman and Leo M. Zimmerman, J. Pharmacol. & Exper. Therap. **48**:301 (July) 1933.

Edema was produced in the hindlegs of dogs by an injection of fibrinogen and cephalin in suspension. The subcutaneous injection of calcium gluconate and parathyroid extract-Collip hastened the disappearance of the edema as compared with that in the controls. The authors think that this is due to the lessened permeability of the capillaries.

Pilcher, Cleveland.

Blood Sugar as Affected by the Psychic Secretion of the Glands of Digestion. G. Sanpaolesi, Riv. di clin. pediat. **31**:1076 (Sept.) 1933.

Observations were made of the sugar and the inorganic phosphorus of the blood of five children between the ages of 10 and 18 months. During fasting the blood sugar was increased in four of the five children approximately 0.02 per cent by the psychic stimulation of seeing food or of sucking an empty bottle. No consistent change was observed in the blood phosphorus under similar stimulus.

Higgins, Boston.

EXPERIMENTAL STUDIES OF THE EFFECT OF ULTRAVIOLET RAYS ON THE FERMENTS IN THE BLOOD OF GROWING ORGANISMS. O. J. KARAPETJAN, Ztschr. f. d. ges. phys. Therap. **45**:8 (July 21) 1933.

From experiments with five puppies irradiated with ultraviolet rays from a mercury vapor arc in quartz, observing the effects on the blood ferments, amylase, catalase and lipase, the author infers that the activity of amylase is greatly increased in proportion to the amount of ultraviolet radiation the animal has received. The same is true with catalase, except that the activity of catalase is incited best by small doses of ultraviolet rays. The fermentative activity of lipase was not found to be perceptibly influenced by ultraviolet radiation. In comparison with unirradiated controls, a smaller increase of weight was observed in puppies subjected to irradiation with the mercury vapor arc in quartz. It was noticeable that of five puppies with pneumonia the controls died, and all those submitted to the ultraviolet irradiation survived.

VINTON, Brooklyn.

## Nutrition

EFFECTS OF VITAMINS A AND D ON ANTIBODY PRODUCTION AND RESISTANCE TO INFECTION. MERIDIAN RUTH GREENE, Am. J. Hyg. **17**:60 (Jan.) 1933.

The serums of rabbits deficient in vitamins A and D were normal in regard to natural hemolytic antibodies for the red corpuscles of sheep. Rabbits deficient in vitamin A exhibited a marked lack of response to immunization with the red cells of sheep or oxen. The titer of the serum of each control animal was from 10 to 300 times higher than that of the corresponding vitamin-deficient rabbit into which injections were made at the same time. Animals deficient in vitamin D responded normally to the red blood cells of sheep. Rabbits deficient in vitamins A and D showed no change in the normal agglutinin content of the serum for Bacillus typhosus. Rabbits deficient in vitamin D showed no difference in normal and acquired hemagglutinins for the red cells of sheep when compared with control animals. Rabbits on diets deficient in vitamins A and D showed no change in the serum complement, and their temperature remained normal during the period of depletion; these animals showed no difference in erythrocyte counts when compared with their controls. Rabbits on a diet deficient in vitamin A reacted with definite leukocytosis, which appeared with xerophthalmia in about 75 per cent of the animals. The leukocyte counts of the rabbits deficient in vitamin D were normal. In the group with xerophthalmia, 53 per cent showed a decided absolute increase in pseudo-eosinophils when compared with the control group. Lymphocytosis occurred in the rachitic animals and their controls, but it occurred in a higher percentage of the rabbits deficient in vitamin D and had a tendency to be considerably greater. After the appearance of xerophthalmia there was a change in the nasal flora of the rabbits deficient in vitamin A. The flora of the vitamin A controls and that of the rachitic group did not change. Spontaneous infections with Bacillus pyocyaneus occurred in rabbits deficient in vitamin A, but not in animals deficient in vitamin D or in the controls of either group. Rabbits deficient in both vitamin A and vitamin D were more susceptible to intranasal infection with Bacterium lepisepticum than control animals. Rabbits deficient in vitamin A were more susceptible to intravenous infection with type I pneumococcus than normal controls. Rachitic rabbits showed a higher morbidity and mortality following intranasal inoculation with type I pneumococcus than the control animals. There are thirty-two references to the literature.

KUGELMASS, New York.

RELATION OF SERUM CALCIUM TO PATHOLOGIC CALCIFICATIONS OF HYPERVITAMINOSIS D. ARTHUR HAM and B. C. PORTUONDO, Arch. Path. **16**:1 (July) 1933.

Following the administration of a single large dose of activated ergosterol to rats and rabbits, the serum calcium level and the histologic appearance of the internal organs were studied. The serum calcium level of rats rose for two or

three days after the ingestion of activated ergosterol and then gradually diminished. Pathologic calcifications did not appear when the serum calcium was rising, but they appeared in large numbers when it was falling. It is assumed that the rise in serum calcium is caused by an attraction of the parathyroid-controlled fraction of the serum calcium for calcium which is obtained from the intestines, bones and other tissues. Likewise, the fall in serum calcium may be caused by a release of calcium from the fraction of the serum calcium controlled by the parathyroid hormone, and since the serum can retain only a small amount of calcium in simple solution, precipitation occurs in the tissues. Necrosis and cellular infiltration of the tissues preceding calcification may occur during the upswing of the serum calcium level because of withdrawal of calcium from the tissues. By this mechanism the toxic effect of large doses of parathyroid hormone and vitamin D can be explained without assuming the portion of the serum calcium associated with the parathyroid hormone to be physiologically active.

LeMaster, Evanston, Ill.

Infant Feeding: The Proprietary Milk Preparations. Samuel Friedman, Arch. Pediat. **50**:261 (April) 1933.

The author classifies the common proprietary foods in general use in the feeding of infants and gives instructions as to the proper preparation of these foods. He believes that frequently a medical student finishes his course in pediatrics with little or no knowledge of the types of proprietary foods on the market and with little understanding as to how these foods are to be administered.

Waddell, Jr., University, Va.

Underfeeding of Infants and Children. George J. Feldstein, Arch. Pediat. **50**:297 (April) 1933.

Attention is called to the tendency on the part of many practitioners to underfeed babies, especially the new-born. Certain fundamental errors in feeding babies and children are pointed out, and stress is laid on the fact that each case must be considered individually and care must be taken to supply adequate amounts of all the food factors.

Waddell, Jr., University, Va.

Raw Basic Feeding in the Prevention and Treatment of Dental Caries. I. Newton Kugelmass and Thomas B. King, Arch. Pediat. **50**:307 (May) 1933.

The author's conclusions are as follows:

1. Dental caries is a syndrome of many systemic and local disturbances rather than a simple disease of single etiology.

2. Determination of the degree of dental caries was made by means of Bodecker's life caries index in children under continuous supervision for other systemic conditions.

3. Children free from dental caries were of the more stable elements of their race, whose general and oral hygiene were superior to those of children with marked dental caries.

4. Dental caries is maximum at the age of 6 for deciduous teeth and at the age of 12 for permanent teeth, the incidence increasing rapidly with age. This rhythm parallels that of development, thus relating dental caries to deep-seated metabolic changes in the growing body.

5. The degree and prevalence of dental caries are unaffected by recurrent infections of the mouth and the upper respiratory tract.

6. Dental caries is neither prevented nor minimized by breast feeding. Children free from dental caries were fed base-forming dietaries in infancy, which contained early additions of semisolids in the first months of life.

7. Children with moderate and extreme dental caries showed inadequate intakes of vitamins B, C and D.

8. Children who were fed ketogenic diets base-forming in their mineral content showed low life indexes for caries, while those who were fed ketogenic diets acid-forming in their mineral content showed marked dental caries.

9. Children free from dental caries showed consistently a dietary intake excessive in alkali-forming minerals, with a preponderance of raw fruits and vegetables.

10. Races immune to dental caries consume sufficient raw alkali-forming fruits and berries to balance the acid-forming fresh fish and raw meat.

WADDELL, JR., University, Va.

PRESERVATION OF HUMAN MILK: VI. PRELIMINARY NOTE ON THE FREEZING PROCESS. PAUL W. EMERSON and WASHINGTON PLATT, J. Pediat. **2**:472 (April) 1933.

Human milk rapidly frozen by dry ice has been kept for several months and then thawed and fed to premature infants with excellent results. Chemical analyses, bacteriologic examination and clinical trials show that the method is perfectly satisfactory in the preservation of human milk. This process, by allowing human milk to be saved at a time when the supply is greater than the demand, makes human milk available at all times. LEMASTER, Evanston, Ill.

PELLAGRA IN A CHILD TWO YEARS OLD. EUGENE T. MCENERY, J. Pediat. **2**:478 (April) 1933.

A fatal case of pellagra occurring in a Mexican boy, aged 2 years, is reported. No fresh fruits, vegetables or meat had been given. Improvement under treatment was progressing slowly except for two severe reactions following exposure to ultraviolet rays, when the child died suddenly. LEMASTER, Evanston, Ill.

STUDIES IN RICKETS: VI. COMPARISON OF THE DEVELOPMENT OF RACHITIC CHILDREN WITH THAT OF CHILDREN IN WHOM RICKETS WAS PREVENTED BY ULTRAVIOLET IRRADIATION. J. VICTOR GREENEBAUM and T. K. SELKIRK, J. Pediat. **2**:711 (June) 1933.

Ten children about 5 years of age whose roentgenograms during infancy had shown severe rickets were compared with twelve children of the same age who were known to have been nonrachitic in infancy. The average weight and height, the bony abnormalities and the abdominal findings were practically the same in the two groups. The incidence of mild malnutrition and dental caries was slightly higher in the rachitic group. It is noteworthy that so little difference could be detected between these two groups. LEMASTER, Evanston, Ill.

BODY BUILD IN INFANTS WITH ACUTE INTESTINAL INTOXICATION. HARRY BAKWIN and RUTH MORRIS BAKWIN, J. Pediat. **3**:36 (July) 1933.

Infants with acute intestinal intoxication were found to have less height, narrower faces, narrower shoulders and smaller chests than healthy infants from the same social environment. The decreased dimensions of the infants with intoxication are probably due to retarded growth. Since a deficient diet leads to retardation of growth, the author suggests a causal relationship between dietary deficiency and acute intestinal intoxication. LEMASTER, Evanston, Ill.

INTRACELLULAR FLUID LOSS IN DIARRHEAL DISEASE. ALLAN M. BUTLER, CHARLES F. MCKHANN and JAMES L. GAMBLE, with the assistance of PAULINE MARSH, J. Pediat. **3**:84 (July) 1933.

Estimations of sodium, potassium, nitrogen, phosphorus and total fixed base were made on the urine and stools of two severely dehydrated infants with diarrhea. Samples of blood serum were also tested for total fixed base, chloride

and carbon dioxide content. In both cases the quantity of potassium in the stools was much larger, in relation to the sodium, than would be expected on the basis of the relatively small value for potassium in gastro-intestinal secretions and extracellular fluids. The excretion of potassium in the urine was also high. When, however, the loss of intracellular fluid calculated from the urine potassium was compared with the loss of fluid as estimated from urine nitrogen, it was found to be much larger. It thus seems that potassium and a corresponding quantity of intracellular water are excreted in the urine to a much greater extent than can be accounted for by the destruction of body protoplasm as measured by the excretion of nitrogen. According to these findings, a loss of intracellular fluid in addition to a loss of extracellular fluid occurs in the dehydration produced by diarrhea.

LeMaster, Evanston, Ill.

Observations on the Effect of Aging on the Potency of Spray-Dried Antiscorbutic Material. Henry J. Gerstenberger, Donalda N. Smith and G. L. Hacker, J. Pediat. **3**:93 (July) 1933.

Spray-dried orange juice, used in a mixture of lactose and orange juice, was found to retain its antiscorbutic potency for fifteen months after manufacture, as was shown by the cure of a group of scorbutic guinea-pigs and one human infant with severe scurvy. Protein S.M.A., an acid protein milk to which 20 cc. of lemon juice is added at the time of manufacture, cured scurvy in six infants when given within from five to twenty-three months after the original preparation of the milk.

LeMaster, Evanston, Ill.

Observations on the Nature and Treatment of Diarrhea and the Associated Systemic Disturbances. W. McKim Marriott, Alexis F. Hartmann and Milton J. E. Senn, J. Pediat. **3**:181 (July) 1933.

During the three year period of 1930-1932, 318 infants with diarrhea were observed at the St. Louis Children's Hospital. In 37 per cent of the cases the condition was due to enteral infections by the dysentery-paratyphoid-colon group of organisms. In this group, 66 per cent of the cases were complicated by parenteral infections, such as bronchopneumonia, otitis media, mastoiditis and pyelitis. Eighty-three per cent of the patients with nondysenteric diarrhea showed definitely recognizable parenteral infections in the rhinopharynx, ears and mastoids at the time of admission to the hospital. In the patients with dysentery, the gastric contents showed a higher acidity than normal, and cultures were negative for colon bacilli, whereas in the nondysenteric group the acidity of the gastric contents was very low, and in almost half the cases colon bacilli were the predominating organisms in the stomach. The mechanism by which diarrhea produces dehydration, electrolyte imbalance, starvation and other secondary disturbances in the body is discussed. Routine methods of treatment for diarrhea are presented in detail.

LeMaster, Evanston, Ill.

The Alleged Correlation Between the Rate of Growth of the Suckling and the Composition of the Milk of the Species. Grover F. Powers, J. Pediat. **3**:201 (July) 1933.

The data of Abderhalden showing an alleged correlation between the rate of growth of sucklings and the protein and ash of the milk of the species are analyzed from the standpoint of the percentage of the total calories in protein, carbohydrate and fat. Additional data similar to those of Abderhalden are also analyzed. According to the author's method of evaluation, there is no correlation between the rate of growth of the suckling and the constituents of the milk. Protein furnishes nearly 20 per cent of the total calories of the milk of a large number of species of animals, but in man it furnishes less than 10 per cent of the total calories of milk. The biologic significance of these facts is obscure.

LeMaster, Evanston, Ill.

THE COMPOSITION OF THE UNSATURATED FATTY ACIDS OF ANIMAL TISSUES. H. G. SMITH, Proc. Iowa Acad. Sc. **38**:171, 1931.

Little information is available as to the composition of the unsaturated fatty acids of animal tissues, especially as regards the location of the double bonds. This article is a report of preliminary experiments on the fatty acids of the muscle of beef heart and those of beef liver. The unsaturated acids were separated by two methods of crystallization of the bromine derivatives and fractional distillation of the methyl esters. The method of Armstrong and Hilditch was used for the oxidation of the unsaturated acids, and the results obtained up to the present indicate that the first double bond nearest the carboxyl group is in the 9:10 position. Azelaic acid is the only dibasic acid which has been separated from the products of oxidation. Evidence of the formation of other dibasic acids has been obtained, but these have not been identified as yet.

KUGELMASS, New York.

THE REACTION OF HUMAN MILK. W. PARTRIDGE, Analyst **58**:88, 1933.

Richmond gives the following values for the acidity of eight samples of human milk: 5.5, 2.8, 3.7, 3.7, 4.7, 9.3 and 5.5 degrees. These would be the conventional dairy degrees of acidity. Results of analyses of fifteen samples made during fourteen years show that the acidity lies in most cases between 2 and 5.5 dairy degrees. Values for the fat, protein, lactose, ash and acidity of the fifteen samples are given.

KUGELMASS, New York.

EVIDENCE OF RICKETS IN MANCHESTER. CATHERINE CHISHOLM, Brit. J. Child. Dis. **30**:83 (April-June) 1933.

One thousand six hundred children, aged from 6 to 24 months, were examined, the diagnosis of rickets being based on physical and roentgen examination; chemical examination of the blood was impracticable since a large number of children had to be examined under outpatient conditions.

Seven and three-tenths per cent of the children showed definite signs of recent rickets on roentgen examination. In a further 21 per cent there were signs suggestive of slight rickets.

The incidence was found to be twice as great in the inner city as outside the 2 mile radius.

No direct and constant correlation between rickets and dentition was observed.

A fifth of the mothers said that cod liver oil was administered, but as to the quantity or regularity there was a good deal of doubt.

LANGMANN, New York.

REDUCTION OF WEIGHT BY DEHYDRATION. MAX PORGES, Brit. J. Phys. Med. **8**:9 (April) 1933.

The author accomplishes reduction in weight by the administration of sulphur water without dietetic restrictions or supernormal physical activity. Reductions in weight were also accomplished by baths alone. He presents the hypothesis of "increased renal activity due to the simultaneous and related reaction of the vessels in the skin and the kidneys."

HARTMAN, Cleveland.

GASTRO-ENTERITIS. LINDSAY MALE, M. J. Australia **1**:364 (March 25) 1933.

The author reviews the types of diarrhea prevalent in Australia, laying particular emphasis on the infectious type. In the treatment he stresses the importance of isolation, both in hospitals and in private practice, and advocates the use of a diet high in carbohydrates for patients with true dysentery. He advocates the use of dextrose solutions administered subcutaneously and makes a plea for the early use of salt solution administered intraperitoneally, which apparently has

not been so favorably received in Australia as in this country. He advocates the use of castor oil early in the course of the infectious diarrheas other than dysentery, and the use of sodium or magnesium sulphate in dysentery. In dietary treatment he advocates the use of lactic acid milk and apparently starts feeding a little earlier than is usually advocated in this country. TENNEY, Madison, Wis.

## Prenatal Conditions

CONGENITAL CYSTIC DISEASE OF THE LUNG. WILLIAM C. POLLOCK and HORACE P. MARVIN, Am. Rev. Tuberc. **27**:59 (Jan.) 1933.

This rare condition is secondary to a narrowing of the main bronchus or bronchi of the involved lobe or lobes, and it is the narrowing which is congenital. The cystic changes resulting are usually more or less stationary, but may be progressive under certain conditions. Usually the bronchus of one lobe only, most frequently the upper, is affected. When so limited, the entire lobe may become cystic without the development of symptoms. When more than one lobe is involved, pulmonary stress may result in dyspnea, cough and similar symptoms. The condition is usually diagnosed as spontaneous pneumothorax. The chief differentiating points are:

(*a*) No history of a sudden onset.
(*b*) Usually no symptoms, except shortness of breath in far advanced cases.
(*c*) No usual cause of spontaneous pneumothorax found.
(*d*) Constant roentgen and physical findings over a long period.
(*e*) Usually no symptoms referable to the chest.
(*f*) Roentgen findings differing from those of pneumothorax in the following particulars:
  (1) There is no displacement of the mediastinum.
  (2) The compressed lung cannot be seen.
  (3) The fine strands traversing the space are in wide sweeping curves and are not straight, as are the adhesions traversing the space in pneumothorax.

If other proof is required, artificial pneumothorax may be established, which differentiates the two conditions readily. EUGENE SMITH, Ogden, Utah.

CONGENITAL ABSENCE OF TESTES (ANORCHIA). VIRGIL S. COUNSELLER and MAURICE A. WALKER, Ann. Surg. **98**:104 (July) 1933.

Few reports of absence of the testes have been made. Therefore, the authors review nine cases reported from the literature and two of their own.

Since the testes may lie within the abdomen or in the inguinal canal without being palpable, it cannot be determined definitely by general examination that both testes are absent. The true anatomic condition can be accurately ascertained only by surgical exploration or by necropsy. The authors discuss the possible causes, but no definite conclusions as to the etiology are reached.

The authors note that hernia is not present in the reported cases of anorchia. They therefore offer the warning that if hernia is absent and the testes are not palpable, it should be remembered that although the testes are probably only undescended, they may be completely absent, and this should be mentioned to the patient or his relatives before orchidopexy is attempted. BANTIN, Omaha.

CONGENITAL VALVES OF THE POSTERIOR URETHRA IN TWINS. I. DAVIDSOHN and CHARLES NEWBERGER, Arch. Path. **16**:57 (July) 1933.

Identical valves in the posterior urethra were found in twins. The valves obstructed the outflow of urine, producing stasis and infection in the bladder, ureters and kidneys. The embryologic significance of the valvular obstructions in the posterior urethra is discussed. LEMASTER, Evanston, Ill.

MULTIPLE CONGENITAL ABNORMALITIES. A. J. BALLANTYNE, Proc. Roy. Soc. Med. **26**:313 (Jan.) 1933.

An infant, 6 days old, was taken to the hospital on account of swelling of the eyelids of the right eye, which had been present since birth, although it had lessened considerably. On examination of the eye, many congenital abnormalities were found. The report is accompanied by pictures of the eye.

WILLIAMSON, New Orleans.

CONGENITAL MORBUS CORDIS IN TWO SISTERS. R. W. B. ELLIS, Proc. Roy. Soc. Med. **26**:511 (March) 1933.

The family history, the results of physical examinations and the findings of the orthodiagrams in the cases of two patients who were sisters, aged 9 and 5 years, respectively, are given in the report. In both cases the diagnosis of patent ductus arteriosus was made, both clinically and by roentgenologic examination.

WILLIAMSON, New Orleans.

CONGENITAL ABNORMALITY OF SPINE. F. W. M. PRATT, Proc. Roy. Soc. Med. **26**:516 (March) 1933.

A case of congenital spinal abnormality is reported in a girl, aged 11½ years. Roentgenograms showed fusion of the first and second dorsal vertebrae, a wedge-shaped third dorsal vertebra, with the base to the left, and eleven ribs on the right side, with probable fusion of the upper second and sixth lumbar vertebrae, resulting from lumbarization of the first sacral vertebra. WILLIAMSON, New Orleans.

CRANIOFACIAL DYSOSTOSIS WITH ECTRODACTYLISM. R. GARCIN, R. THUREL and P. RUDAUX, Arch. de méd. d. enf. **36**:359 (June) 1933.

This curious form of hereditary dystrophy has occasionally been described in the literature under the name of Crouzon's disease. The symptomatic triad consists of cranial deformity resembling oxycephaly; facial malformation, particularly of the nose and jaw, and exophthalmos with divergent strabismus. The authors report a case in an Armenian child aged 23 months. AMESSE, Denver.

CONGENITAL CAVERNOUS ANGIOMA OF THE LIVER. ENRIQUE ADALID and FLORENCIO ESCARDO, Arch. argent. de pediat. **3**:728 (Nov.) 1932.

An exceedingly rare condition, congenital cavernous angioma of the liver, occurred in a new-born infant. Increasing pallor and recurrent attacks of cyanosis and progressive dyspnea, combined with the presence of a large irregular mass in the upper part of the abdomen, pointed to an acute abdominal condition probably accompanied by extensive hemorrhage. Laparotomy revealed a large angioma of the left lobe of the liver, with extensive hemorrhage into the abdomen. The case ended fatally. Early operative procedure is always indicated in this condition but is rarely successful. SCHLUTZ, Chicago.

CONGENITAL MALFORMATION OF THE HEART IN INFANCY. R. PEREIRAS, Arch. de med. inf. **1**:298 (Sept.) 1932.

A boy, aged 13, had dyspnea, cyanosis and polycythemia. The case would fall into the group designated as the "tetralogy of Fallot," except that there was no enlargement of the pulmonary area. SANFORD, Chicago.

OBSERVATIONS ON PREMATURE INFANTS. S. FALCON, Arch. de med. inf. **2**:83 (March) 1933.

Premature children fall into two categories: simple premature children and those tainted by inheritance. The simplest form of maintaining heat is an open cradle

surrounded by hot water bottles. The only form of food advisable is mother's milk, which should be extracted by an electric breast pump, if necessary.

SANFORD, Chicago.

CONGENITAL HEART DISEASE. L. T. BARBOSA, Rev. brasil. de pediat. **1**:27 (April) 1933.

A case of congenital heart disease in a boy, aged 1 year, is described. The physical signs were characteristically a thrill over the precordial area and a systolic murmur that is described as a "jet of steam." A roentgenogram showed an enlarged globular heart. The author concludes that this is a typical case of interventricular communication, as described by Roger.

SANFORD, Chicago.

URIC ACID AND BILE PIGMENT CONCENTRATIONS OF THE CORD BLOOD. G. BERGER, Ztschr. f. Kinderh. **54**:196, 1933.

In 120 determinations on the blood of the umbilical cord, the values for uric acid were from 2.68 to 8.48 mg. per hundred cubic centimeters (average, 4.97), and those for bile pigment, between 0.81 and 3.37 mg. (average, 1.6). There was no relation between the levels of the two substances.

SHELLING, Baltimore.

A CASE OF TERATOMA OF THE NECK. E. PETERSON, Acta obst. et gynec. Scandinav. **13**:1, 1933.

Teratomas of the neck are rare. They are usually located on the lateral surface in the region of the thyroid gland and are very large, often exceeding the size of the baby's head. These tumors are frequently mistaken for cystic goiters, but are always entirely independent of the thyroid gland and never display any of the characteristics of thyroid tissue.

Grossly, these tumors are fluctuating, irregular masses, containing many cysts of varying sizes and consistency. Microscopically, they are extremely variable, but in the main they are derived from the three embryonic layers, as are teratomas elsewhere in the body. These tumors are of interest to the obstetrician because they render delivery of the child exceedingly difficult and usually necessitate a mutilating operation.

The case reported presented the following features: Labor was successfully induced by artificial rupture of the membranes. After a fifteen hour and ten minute labor, a female stillborn infant was delivered without a great deal of difficulty because of the small size of the fetus, which weighed 1,730 Gm. and was 39 cm. in length. There were no signs of maceration.

The tumor was 12 by 9 cm. and was continuous with the esophagus and larynx. It was both solid and cystic, containing one large cyst and several smaller ones. Microscopically, one noted glandular epithelium, hyaline cartilage, a few lymphocytes and a fibrocellular stroma in the solid portion of the tumor. The cysts contained a necrotic hemorrhagic substance. No signs of malignancy were noted.

ADAIR, Chicago.

## Diseases of the New-Born

CONGENITAL GOITER. ALBERT L. HILL, Arch. Pediat. **50**:424 (June) 1933.

A case of congenital goiter is presented in which the gland, with a small piece of trachea, weighed 57 Gm.; the child died on the fourth day of life with some signs of thyrotoxicosis—high temperature, rapid pulse and symptoms of pressure on the trachea. The ovary showed some signs of too early maturation of the follicles.

Attention is also called to the frequency of congenital goiter in so-called goiter belts. The cause of congenital goiter appears to be lack of iodine. The mortality varies, children living for more than from twenty-four to thirty-six hours having a fair chance of recovery.

WADDELL, JR., University, Va.

THE BRONCHIAL TREE IN THE DECOMPOSING LUNG OF THE NEW-BORN. A. FOERSTER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:420, 1933.

The determination of the occurrence of spontaneous respiration is difficult in decomposing pulmonary tissue of the new-born. By using Weigert's elastic tissue stain the bronchial tree may be readily demonstrated, even when other tissue elements are disintegrated. On the basis of the examination of sixty lungs of new-born infants and from the patients in four medicolegal cases, the author concludes that the method satisfactorily demonstrates the bronchial tree, which is fully expanded when respiration has taken place. However, the diagnosis must not be made on one section, but should include a study of the lung from the hilus to the periphery.

KLEIN, Chicago. [ARCH. PATH. ]

SIMULTANEOUS STUDIES OF BILIRUBIN IN THE BLOOD, ERYTHROCYTES AND HEMOGLOBIN IN ICTERUS NEONATORUM. PAAVO HEINIÖ, Acta pædiat. **14**:474 (July 12) 1933.

The author reports simultaneous studies of the bilirubin content of the serum, the percentage of hemoglobin, the red cell count, the weight of the child and the reticulocyte values in nine newly born infants from the first day of life to the forty-fifth day. During the first few days the estimations were made daily, thereafter at longer intervals.

In eight cases the concentration of bilirubin in the blood increased rapidly during the first few days, and then fell, at first rapidly then more gradually, reaching its normal value within two or three weeks. The time of appearance, the degree and the duration of jaundice bore a close relationship to the concentration of bilirubin. In one case in which the concentration of bilirubin did not reach high values jaundice was absent.

In all cases the hemoglobin concentration and the red cell count fell rather sharply during the first few days. This drop was followed by a brief rise, proportional to the degree and to the rate of loss of body weight which occurred during the first few days of life. After this, both the hemoglobin and the number of red cells decreased regularly until the end of the period of observation.

In the majority of cases there was a definite inverse proportionality between the degree and the rate of decline in hemoglobin and red cells and the increase in bilirubin in the blood and the appearance of jaundice. In a few cases such a relationship was definitely not present.

The number of reticulocytes was regularly high during the first few days of life and then decreased gradually during the ensuing week or two, rising again toward the end of the period of observation. There was no regular relationship between the number of reticulocytes and the concentration of bilirubin.

These observations suggest that neonatal hyperbilirubinemia and jaundice depend on accelerated neonatal destruction of the blood and on another factor independent of this. This second factor seems to be a relative inability of the liver to keep pace with the increased quantity of the bilirubin, which it is called on to excrete.

MCCUNE, New York.

## Acute Infections

GUIDEPOSTS ALONG THE ROAD THAT LEADS TO THE DIAGNOSIS OF THE MORE COMMON ERUPTIVE DISEASES. JOHN RANDOLPH GRAHAM, Arch. Pediat. **50**:223 (April) 1933.

The author reviews the usual eruptive fevers and points out the most important symptoms in diagnosis. Attention is called to the fact that, with unimportant exceptions, little advance has been made in the diagnosis of common eruptive fevers since 1900.

WADDELL, JR., University, Va.

DIPHTHERIA IMMUNIZATION RECORDS: WHY THEY SHOULD BE KEPT AND USED. Health News (New York) **9**:209 (Dec. 26) 1932.

E. S. Godfrey, of the State Department of Health, urges that health officers secure more accurate figures on immunization. "Estimating" leads to error, especially in failing to show how many persons received injections or how many received complete series of injections.

AIKMAN, Rochester, N. Y.

THE USE OF CONVALESCENT SERUM FOR THE PREVENTION AND ATTENUATION OF MEASLES. S. O. LEVISON, C. MCDOUGAL and WILLIAM THALHIMER, Illinois M. J. **43**:258 (March) 1933.

Since the first report on the use of human convalescent serum in measles there have been numerous reports in the literature on the effectiveness of this method in either preventing or modifying the disease. With only a rare dissenting report, a mass of literature has accumulated affirming the successful prophylactic use of measles convalescent serum. There is considerable variation in the number of cases in which complete protection was obtained, the figures ranging from 48 to 97 per cent. However, when the instances of attenuation of measles are included in the favorable results, there is a consistent uniformity of success in more than 90 per cent of the cases.

Despite some adverse opinion, many favorable reports have also appeared on the use of normal adult serum and of whole blood as an effective and readily accessible substitute for convalescent serum to be used for the prevention of measles. The number of both completely protected patients and those with modified cases is distinctly lower than for persons given serum from recent convalescents. Pooled normal adult serum seems to be more potent than whole blood. The adult serum seems relatively effective for prophylaxis in doses of from 20 to 40 cc., and the whole blood in doses of from 40 to 80 cc. Levinson and his associates treated 287 persons who had come in contact with measles with measles convalescent serum, with complete protection in 60 per cent and attenuation of the disease in 33 per cent of the cases. Serum from patients who had measles two or three months previously seemed to be as protective as that from recent convalescents. Twenty-five patients who had come in contact with measles received adult pooled normal serum; there was complete protection in 56 per cent and sero-attenuation in 40 per cent. The authors believe that it is preferable to allow the development of sero-attenuated measles, with its resultant active immunity, except in sick or puny patients.

BARBOUR, Peoria, Ill.

FURTHER EXPERIENCES WITH INTRAVENOUS ANTITOXIN TREATMENT OF SCARLET FEVER. H. STANLEY BANKS, J. Hyg. **33**:282 (April) 1933.

This report of 800 cases of scarlet fever in which the patients were treated by intravenous administration of scarlatinal antitoxin without fatality, supplements one in 1929 of 404 cases in which the patients were similarly treated. The total of 1,204 cases were based on personal experience.

Complications, desquamation, duration of residence in the hospital, cross-infections and relapses have been at a surprisingly low level since initiation of the treatment four and one-half years ago. Compared with the previous record, the mortality has dropped from 1.05 to 0.08 per cent; the total complications, from 33 to 5.2 per cent, and the average stay in the hospital, from forty-six to sixteen and six-tenths days. The rapid arrest was indicated by the disappearance of toxemic symptoms in from six to twelve hours, subsidence of faucial edema in twelve hours and the fading of the rash in from twelve to twenty-four hours.

From 10 to 20 cc. of the serum was given, depending on the age. The usual precautions against reactions and the usual contraindications were observed. Especial care was used with new batches of serum. Anaphylactic reaction was not met with in this series. Thermal reactions in about three fourths of an hour

were common but not dangerous, just as in the case of serum sickness, the total being 33 per cent. Serum from several commercial houses was used.

JANNEY, Milwaukee.

WHOOPING COUGH COMPLICATED WITH INTUSSUSCEPTION. ROY M. GREENTHAL, J. Pediat. **2**:299 (March) 1933.

An infant, aged 3 months, with active whooping cough, was admitted to the hospital because of vomiting, pain and bloody stools. An abdominal mass was easily palpated. An immediate operation under ether anesthesia showed an ileocecal intussusception, which was reduced with difficulty. One week after the operation following a paroxysm of severe coughing, the wound broke open and a loop of intestine protruded. This was replaced, and the incision was sutured. Except for a moderate abdominal hernia, there was complete recovery.

LEMASTER, Evanston, Ill.

VARIATIONS IN THE REACTION TO THE SCHICK TEST. MEREDITH B. HESDORFFER, J. Pediat. **2**:318 (March) 1933.

Of 2,098 university students on whom Schick tests were performed, the 3 plus and 4 plus positive reactions occurred in 39.54 per cent of those whose skins were highly pigmented, in 17.92 per cent of those with moderate pigmentation of the skin and in 21.40 per cent of those with little or no pigmentation. Nine persons with positive reactions were tanned by ultraviolet irradiation on a part of the cutaneous surface, and Schick tests were repeated on the tanned region and on the unexposed skin. In 8 of these persons the reaction was more severe on the tanned area than on the pale area.

LEMASTER, Evanston, Ill.

DIPHTHERIA IMMUNIZATION WITH CONCENTRATED TOXOID INTRADERMALLY. ALTON GOLDBLOOM and DAVID L. KLEIN, J. Pediat. **3**:112 (July) 1933.

Diphtheria toxoid, concentrated by precipitation with acetic acid so that 0.2 cc. was equivalent to 1 cc. of ordinary toxoid, was given by intradermal injection to immunize children with positive reactions to the Schick test. Some of the children showed negative reactions at the end of two weeks and, in one case, as early as seven days after one injection of the toxoid. Children who were highly sensitive to the toxoid were more rapidly immunized than those with little or no sensitivity, as was evidenced by the degree of reaction. Persons with a moderately high antitoxin titer in the blood were readily immunized, but in those having extremely low titers it was difficult and sometimes impossible to produce immunity. This work represents an attempt to develop a rapid method for active immunization. The authors believe that the study so far points to the necessity of larger doses and to the importance of the production of sensitivity to toxoid in order to obtain good results.

LEMASTER, Evanston, Ill.

MEASLES IN NEWBORN INFANTS. (MATERNAL INFECTION). JEROME L. KOHN, J. Pediat. **3**:176 (July) 1933.

Four cases of measles in very young infants infected by their mothers have occurred at Willard Parker Hospital during the past two years. In two of the cases the mothers were in the incubation period of measles at the time of delivery. The infants showed fever followed by a typical course of measles on the ninth and tenth days, respectively, after the onset of the mother's illness. Two infants were born while their mothers were in the eruptive stage of measles. Measles failed to develop in one after an injection of convalescent serum, even though he was kept with his mother. The other infant was merely isolated from his mother and also showed no signs of measles. Another infant, who was born while his mother was in the incubation stage was apparently protected by convalescent serum. Since the course of measles in young infants is usually severe, the use of convalescent serum soon after exposure is indicated.

LEMASTER, Evanston, Ill.

TREATMENT OF INFECTIOUS DISEASES IN CHILDREN. JULIAN P. PRICE, J. South Carolina M. A. **29**:148 (June) 1933.

The author briefly discusses the treatment of five different infectious diseases from a practical standpoint. The five are: pneumonia, bacillary dysentery, tetanus, epidemic meningitis and diphtheria. In treating pneumonia, emphasis is laid on rest, plenty of fluids, fresh air and stimulants, when needed. Lobar pneumonia is much more common in infants than is realized. Transfusions may be life-saving measures in some cases, but are too frequently given in cases of pneumonia.

Price states that in most cases of infectious diarrhea the dysentery bacillus can be isolated from the stool. Fluids should be used freely, and 5 per cent solutions of dextrose or 4 per cent solutions of sodium bicarbonate should be given. Saline solution injected intraperitoneally or intravenous transfusions are used successfully. In the second stage a bland diet or one suitable for the treatment of patients with typhoid is advised, with sour milk instead of sweet milk. Drugs are seldom beneficial.

The early diagnosis of tetanus is necessary for successful treatment with antitetanic serum, which should be given intraspinally the first day and subsequently intravenously, diluted with physiologic solution of sodium chloride. Early signs are rigidity of the spinal muscles and the complaint of backache when the patient jumps on his heels.

The early use of antimeningococcic serum is paramount in the treatment of meningococcic meningitis. Administration of the serum by the cisternal route is not sufficiently safe to be advocated frequently.

The eradication of diphtheria can be accomplished by the widespread use of toxoid or toxin antitoxin. The early diagnosis of diphtheria and the immediate administration of antitoxin are essential to cure. In laryngeal diphtheria the author proposes the following treatment in the order named: (1) suction of the membrane, (2) intubation and (3) tracheotomy. WESTON, JR., Columbus, S. C.

SMALLPOX AND VACCINATION. SAMUEL B. WOODWARD, New England J. Med. **208**:641 (March 23) 1933.

The author makes a plea for compulsory vaccination in all schools, public, private or parochial, and cites the results obtained in New York, where teachers, janitors and scrub women also must be vaccinated. As a result, there was only one death from smallpox in twenty years. In contrast, the author reports that in the state of Utah, in which compulsory vaccination is prohibited, there are among the 434,000 inhabitants almost as many cases of smallpox as there are in Russia, with a population of 180,000,000. GENGENBACH, Denver.

THE DIAGNOSIS OF MILD SMALLPOX AND SCARLET FEVER. CHARLES ARMSTRONG, New England J. Med. **208**:1257 (June 15) 1933.

The author first discusses the differential diagnosis between mild smallpox (variola minor) and ordinary chickenpox, emphasizing the clinical history and the distribution and character of the lesions. In doubtful cases he suggests three laboratory procedures:

In the Tieche test, material collected from the suspected lesions is macerated in a little saline solution and heated to 80 C. for fifteen minutes (or may even be boiled). This heated material is then used as a vaccine on the skin of a well vaccinated subject, usually the diagnostician himself. If the case is one of smallpox, a reaction of immunity should result. In the Paul test, material from suspected lesions is placed on the scarified cornea of a guinea-pig. If the suspected lesions are those of smallpox, corneal ulcers may develop within from forty-eight to seventy-two hours. In the complement-fixation and flocculation tests, a suspension from suspected lesions is employed as an antigen against an antiserum prepared from vaccine-immune rabbits. Or, in cases seen during later stages of the disease, serum from the patients may be tested for its complement-binding or flocculating power against suspensions of vaccine virus.

Mild rashes of scarlet fever are also discussed. Additional tests suggested are: isolation of hemolytic streptococci from the throat; the Schultz-Charlton blanching test; the Dick test during convalescence in a child previously tested. Pastia's sign and the Rumpel-Leede test are not considered specific for scarlet fever.

GENGENBACH, Denver.

POLIOMYELITIS. MURRAY B. GORDON, New York State J. Med. **32**:1362 (Dec. 1) 1932.

A committee on poliomyelitis composed of fourteen members of the Medical Society of the County of Kings has been making a study of the epidemic which occurred in 1931 in the borough of Brooklyn. There were 2,325 cases, with a mortality of 10 per cent. In 1916, 4,312 cases were reported, with 1,147 deaths, or 26.6 per cent.

Clinical records of both hospital and private cases are being studied in an attempt to evaluate various methods of active treatment and after-care. The Drinker respirator was used in 65 cases. Sixteen of these patients are still living and "practically all have almost complete paralysis."

AIKMAN, Rochester, N. Y.

RUBELLA. JOHN RANDOLPH GRAHAM, New York State J. Med. **32**:1368 (Dec. 1) 1933.

The author gives a general description of rubella, dealing especially with the differential diagnosis.

AIKMAN, Rochester, N. Y.

RELATIVE ADVANTAGES OF TOXIN-ANTITOXIN AND TOXOID. WILLIAM A. HOLLA, New York State J. Med. **32**:1413 (Dec. 15) 1932.

One thousand five hundred children who had received three doses of toxin-antitoxin during the period from 1927 to 1931 were recently given Schick tests, and only 67 per cent were immune. The Westchester Department of Health recently used toxoid, in three injections of 0.5 cc. at weekly intervals, and found that about 97 per cent of the children acquire immunity.

AIKMAN, Rochester. N. Y.

THE SHWARTZMAN PHENOMENON: FACTORS COMPLICATING ITS USE IN THE TESTING OF ANTIMENINGOCOCCIC SERUM. ANNA M. PABST and SARA E. BRANHAM, Pub. Health Rep. **48**:639 (June 9) 1933.

In 1928 Shwartzman reported an interesting phenomenon. Rabbits were given intracutaneous injections of filtrates of cultures of typhoid bacilli. Twenty-four hours later they were given intravenous injections of the same material. Within from four to five hours after the second injection many of the rabbits showed pronounced hemorrhagic necrosis at the site of the intracutaneous dose. The same phenomenon has been observed with filtrates of meningococci and other bacteria. Shwartzman obtained neutralization of the reaction to the meningococcic filtrate by meningococcic immune serum and suggested the practical application of this principle in the evaluation of antimeningococcic serum.

The authors repeated the work of Shwartzman. They found that the reactions produced by meningococcus filtrates were not always neutralized by antimeningococcic serum but were frequently neutralized by antipneumococcic, antidysenteric and antigonococcic serums. The nonspecific neutralization was observed so frequently that considerable doubt was felt as to the usefulness of the Shwartzman phenomenon in the evaluation of therapeutic antimeningococcic serum.

LEMASTER, Evanston, Ill.

THE RELATIONSHIP BETWEEN THE VIRUSES OF ZOSTER AND VARICELLA AS DEMONSTRATED BY THE COMPLEMENT-FIXATION REACTION. R. T. BRAIN, Brit. J. Exper. Path. **14**:67 (April) 1933.

The serum of persons convalescent from zoster and varicella contains specific antibodies, which can be demonstrated by complement fixation, the vesicle fluid being used as antigen. Fluid from zoster vesicles gives equally good fixation with zoster and with varicella serum, and the same is true of the fluid from varicella vesicles. These findings are in conformity with those of Netter and his colleagues in France. They seem to indicate the close relationship and possible identity of the viruses of zoster and varicella. CORNBLEET, Chicago. [ARCH. DERMAT. & SYPH.]

PREVENTION OF POLIOMYELITIS. SIMON FLEXNER, Brit. M. J. **1**:132 (Jan. 28) 1933.

This article is an abstract of the John M. Anders lecture on poliomyelitis, which was delivered before the College of Physicians, Philadelphia, on Jan. 6, 1932.

"From the evidence presented to date, poliomyelitis is a particular form of infection of the upper respiratory tract, and in harmony with other epidemic diseases of respiratory origin the cases arising during an epidemic cover a wide latitude in degree of symptoms and pathological effects." The number of cases of specific infection with this disease is very large. The number showing paralytic sequelae varies with the epidemic but is relatively small. At least in monkeys, any degree of actual infection protects from the effects of the second administration of the virus. In the blood of both human beings and monkeys who have recovered from an attack of poliomyelitis the existence of neutralizing antivirus bodies has been demonstrated. "A mixture consisting of the virus of poliomyelitis and the serum of the blood (of convalescents) was injected into monkeys. No symptoms of the disease tended to arise from this injection."

The blood of recovered monkeys is weaker in antivirus substances than is the blood of recovered human beings. As a result of neutralizing experiments in vivo, it has been found that when the virus is injected not longer than from eighteen to twenty-four hours before the serum and when the amount of virus introduced into the brain does not exceed a fixed quantity, neutralization in vivo can be accomplished. Symptoms following neutralization may be shown to be nil or very faint and partial. Medical opinion is still divided whether serum is effective, even in the preparalytic stage of poliomyelitis, to any great extent. Passive protection by means of serum has been achieved, and in the course of severe outbreaks of epidemic poliomyelitis, convalescent human serum can be employed to afford passive protection to persons, especially children, who are menaced by the disease. The procedure is to withdraw blood from parents under sterile conditions and to inject 30 cc. or more of the uncoagulated blood intramuscularly.

ROYSTER, University, Va.

PREVENTION OF MEASLES BY CONVALESCENT SERUM. THOMAS M. HUNTER, Brit. M. J. **1**:217 (Feb. 11) 1933.

The author describes his experience with the use of convalescent serum in the prevention of measles, with special reference to the efficacy of relatively small doses.

ROYSTER, University, Va.

MUMPS AND APPENDICITIS. BARBARA FINCH, Brit. M. J. **1**:315 (Feb. 25) 1933.

A case of mumps complicated by appendicitis is reported, in which the author believes that there was a direct etiologic connection.

ROYSTER, University, Va.

SERUM THERAPY IN POLIOMYELITIS. JEAN MACNAMARA, Brit. M. J. **1**:526 (March 25) 1933.

This article is a general discussion of serum therapy in poliomyelitis including the variations in the potency of the serum, the difficulties in gaging its value and the points which are yet to be learned in regard to this subject.

ROYSTER, University, Va.

THE AETIOLOGY OF ACUTE RHEUMATISM. BERNARD SCHLESINGER, Brit. M. J. **1**:697 (April 22) 1933.

The author discusses the influence of infection, the various theories of streptococcic infection, the theory of allergic influence and the predisposing causes in acute rheumatism. He mentions briefly rheumatoid arthritis.

ROYSTER, University, Va.

EPIDEMIOLOGICAL STUDY OF SCARLET FEVER IN ENGLAND AND WALES SINCE 1900. HILDA M. WOODS, Medical Research Council, Special Report Series, no. 180, London, His Majesty's Stationery Office, 1933.

This monograph consists of a careful and thorough statistical study of scarlet fever in England and Wales. The data analyzed were taken chiefly from the records of the Registrar-General and of medical officers of selected towns. Deaths from scarlet fever have notably diminished during the past thirty years, owing essentially to the lessened severity of the disease. During the period studied no evidence was found to prove that isolation in hospitals has been effective in reducing the prevalence of or the mortality from scarlet fever. In London scarlet fever has been more prevalent in the overcrowded areas, but in Birmingham the greatest incidence was found among the artisan dwellers of the better class. In London there was a significant association between wet years and low prevalence of scarlet fever, but this was not found in other cities. Although the mortality has greatly decreased, the prevalence of scarlet fever has changed little. In London and Manchester the peak of incidence was at 5 years, but local differences were found in other communities. The disease is more common in late autumn and in winter than formerly. The greatest risk of death is in persons under 1 year of age, although the chance of an attack is least in infants.

LE MASTER, Evanston, Ill.

POLIOMYELITIS. B. SANCHEZ, Arch. de med. inf. **1**:308 (Sept.) 1932.

A case of Heine-Medin's disease in a boy, aged 9 years, is discussed. The author emphasizes the necessity of a positive diagnosis to distinguish the condition from allied disorders. All the usual methods of treatment are discussed.

SANFORD, Chicago.

INFANTILE TETANUS. L. E. BRAVO, Arch. de med. inf. **1**:321 (Sept.) 1933.

Sixteen cases of infantile tetanus were studied. Thirteen patients recovered entirely, two were withdrawn from the hospital by relatives before complete recovery, and one died. Fifteen of the patients were boys, and one was a girl. Each patient was treated by large doses of antitetanic serum administered intravenously and intramuscularly (from 30,000 to 40,000 units). The degree of fever does not appear to have any effect on the prognosis; many patients with severe cases have only a slight fever. Magnesium sulphate was given for the convulsions.

SANFORD, Chicago.

TREATMENT OF TETANY BY INTENSIVE SERUM THERAPY. C. PERNETTA and A. PINTO, Rev. brasil. de pediat. **1**:12 (Jan.-Feb.) 1933.

The authors gave a boy, aged 7 years, who was admitted to the hospital in convulsions, 230,000 units of antitoxin during four days. He recovered. They

recommend local cauterization, the application of permanganate dressing to the wound and the administration of chloroform to allay the convulsions in tetany. Antitoxin should be given until the symptoms subside, in doses, roughly, of from 20,000 to 60,000 units per day. The first dose is given intraspinally and the remainder subcutaneously.

SANFORD, Chicago.

DIETETIC HANDLING OF DYSENTERY. LISELOTTE LENNHOFF, Monatschr. f. Kinderh. **58**:130, 1933.

The author has tried various treatments for infectious diarrhea in Dusseldorf during the last six years. She finally adopted the following method: For the first twelve to twenty-four hours, a diet of tea is given. For the next two days, the Moro diet of apple purée is used exclusively. Following that, sour milk is given. This diet is not suited for infants under 8 months of age.

GERSTLEY, Chicago.

DIPHTHERIA OF THE GLANS PENIS, THE SCALP AND THE PHARYNX IN THREE CHILDREN OF ONE FAMILY. PETER DAHR, München. med. Wchnschr. **80**:921 (June 16) 1933.

The first child in the family to come under observation was a 5 year old boy in whom diphtheritic balanitis developed. The diagnosis was not thought of at first, and thirteen days after the onset a positive culture of diphtheria bacilli was obtained from the membrane-covered ulcers on the foreskin. Four thousand units of diphtheria antitoxin was given, and the lesions gradually healed.

Two weeks after the first child was taken ill his brother, aged 1 year, was admitted to the hospital because of a gastro-intestinal upset. In addition, he had ulcers on the scalp varying in diameter from 1 to 3 cm. The ulcers were covered with granulation tissue, but no definite membrane was present. Smears from these lesions produced a pure culture of diphtheria bacilli.

Twelve days after the second child was admitted to the hospital typical pharyngeal diphtheria developed in a sister. Bacilli from all three patients were virulent and had identical cultural characteristics.

BRAHDY, Mount Vernon, N. Y.

SCARLATINAL STREPTOCOCCI. H. SCHMITZ, München. med. Wchnschr. **80**:975 (June 23) 1933.

Most authors do not accept the hemolytic streptococcus as the sole cause of scarlet fever. However, it is generally conceded that it plays an important rôle in the pathogenesis of the disease. Schmitz took cultured smears from the nose and throat of patients with scarlet fever. A total of 5,268 smears were taken; approximately 14 per cent of those from the throat and 3.4 per cent of those from the nose were positive for hemolytic streptococci. The culture medium was 5 per cent human blood agar.

These results throw further doubt on the etiologic significance of hemolytic streptococci. Moreover, streptococci are found in the throats of well persons and of those with diseases other than scarlet fever. Herzberg found hemolytic streptococci in the throat cultures of 70 per cent of the children in a clinic for patients with tuberculosis. It is not advisable to base the termination of isolation of the patients with scarlet fever on the bacteriologic examination of smears from the nose and throat.

BRAHDY, Mount Vernon, N. Y.

WHOOPING COUGH. A. SUNDAL, Acta pædiat. **14**:104 (Nov. 30) 1932.

The importance of whooping cough in Norway is attested by the fact that in several recent years it has caused more deaths than measles, diphtheria and scarlet fever combined. Using the clinical material of the Oslo municipal hospital, the

author set out to investigate the duration of the infective stage, the relationship of the whooping cough to activation of tuberculosis and the therapeutic value of vaccines and intramuscular injections of ether.

Cough plate cultures were made at regular intervals in twenty cases and were examined for Haemophilus pertussis. In no instance were these organisms recovered after the fourth week of the disease, counting from the onset of the whooping.

During the whooping cough, four of five tuberculous patients showed a diminution in response to the Pirquet test. (The evidence here is not clearcut, since quantitative methods were not used.) Serial roentgenograms were made in all five patients; in one there was a lighting up of the local process in the lung, with the development of transient râles, an increase in the reaction to the roentgen rays about the focus at the left base and about the hilus, the appearance of pleural exudate and, finally, a regression of the perifocal reaction and a residuum of calcium density at the primary focus and its satellite hilar node.

Intramuscular injection of 1.25 cc. of ether appeared to cause a diminution in frequency and severity of paroxysms in the ensuing twelve hours. The results with the use of vaccines were equivocal.

McINTOSH, New York.

SCARLET FEVER. G. ZUELZER, Acta pædiat. **14**:128 (Nov. 30) 1932.

The author has devised a technic of percussion whereby he claims to demonstrate enlargement of the liver and spleen during the period of incubation in typhus fever and scarlet fever. In scarlet fever the enlargement diminishes or disappears with the development of fever. Atypical, subclinical infections with the virus of scarlet fever may be detected among those coming in contact with a manifest case; and since the author believes that the primary etiologic factor in scarlet fever is a protozoan, the streptococcus being merely a secondary invader, he uses quinine with invariable success in forestalling the development of frank, typical scarlet fever. He also recommends quinine as virtually a specific remedy in fully developed cases, the results being better the earlier the quinine is given.

The arguments embodied in this paper are entirely unconvincing to the reviewer.

McINTOSH, New York.

## Internal Diseases

LIPOID HISTIOCYTOSIS. SYLVAN H. ROBERTSON and SHIELDS WARREN, Arch. Path. **15**:193 (Feb.) 1933.

An Italian girl, aged 2 years, had painless enlargement of the cervical lymph glands of five months' duration. In sections of a gland obtained for biopsy, cells typical of lipoid histiocytosis were seen. High voltage roentgen therapy was administered, and a diet low in fat and high in carbohydrate was advised. Six months later the child was in good health, but the cervical nodes were still involved.

LEMASTER, Evanston, Ill.

RETENTION OF CONGO RED IN AMYLOID DISEASE. MAURICE A. F. HARDGROVE, Arch. Path. **15**:238 (Feb.) 1933.

A woman, aged 47, had chronic nonsuppurative polyarthritis for four years. The course of the disease was one of progressive weakness, persistent albuminuria and edema, without elevation of the blood pressure. The congo red test was performed one hundred and five days and again eighty-four days before death. On both occasions 56 per cent of the dye disappeared from the blood stream in one hour, and none was found in the urine. At autopsy amyloid deposits colored by congo red were found in the spleen and suprarenal glands and, to a lesser degree, in the kidneys and liver.

LEMASTER. Evanston. Ill.

PATHOLOGY OF BRONCHIECTASIS. I. H. ERB, Arch. Path. **15**:357 (March) 1933.

A pathologic study of thirteen cases of bronchiectasis is presented. In eleven of these the lungs were obtained at autopsy; in the other two cases lobes were removed at operation. The histories indicate some type of acute disease of the respiratory tract as the cause of the bronchiectasis. The essential lesion is acute ulcerative bronchitis with destruction of the bronchial wall. The destructive process is favored by mechanical obstruction. Highly vascular granulation tissue develops around the bronchial lumen, which later becomes lined with stratified epithelium. After the bronchi become relined with epithelium, healing is no longer possible.

LEMASTER, Evanston, Ill.

PAROXYSMAL HEMOGLOBINURIA: REPORT OF CASES, WITH FAMILIAL FINDINGS. FRANCIS P. MCCARTHY and ROBERT WILSON, JR., New England J. Med. **207**:1019 (Dec. 8) 1932.

Of the many manifestations of late congenital and acquired syphilis, one of the most striking and one which is probably often overlooked is the syndrome of paroxysmal hemoglobinuria. The prodromal symptoms are chilliness, malaise, pain in the muscles of the back, legs or abdomen and paresthesias of different parts of the body. There is an abrupt rise in temperature to from 101 to 103 F.; this is followed after a short time by a desire to urinate and by the passage of dark red urine. The color commonly persists in the first two specimens of urine and then disappears entirely. The temperature falls, and recovery is complete. There are no symptoms between attacks.

An autohemolysin activated by exposure of the patient to local or general cold is responsible for the phenomena found in this disease. The changes in the blood were first brought to light by Donath and Landsteiner by the demonstration in vitro of the autohemolysin present in the blood serum in a group of cases. The technic of the serologic test is described. The clinical method for the artificial production of an attack, the Rosenbach test, consists in immersing the patient's feet in ice-cold water for about ten minutes to reproduce the symptoms of the disease with or without hemoglobinuria.

Two cases are reported, one in a young adult and the other in a girl whose serum gave positive reactions to the Wassermann and autohemolysin tests. The child had interstitial keratitis, which improved under treatment with neoarsphenamine, and the spontaneous attacks of paroxysmal hemoglobinuria ceased. The girl's mother was under treatment for syphilis. Two younger children, aged 3 years and 20 months, respectively, had negative Wassermann reactions, but their serum reacted positively to the autohemolysin test.

GENGENBACH, Denver.

WHAT IS NEPHROSIS? HENRY A. CHRISTIAN, New England J. Med. **208**:129 (Jan. 19) 1933.

Nephrosis is the name of neither a disease entity nor a definite pathologic lesion. Two clinical characteristics dominate the picture: edema and albuminuria. The author thinks that nephrosis is convenient as a name for a clinical syndrome which is but a phase of the disease glomerulonephritis.

GENGENBACH, Denver.

TREATMENT OF SUBACUTE HEMORRHAGIC NEPHRITIS WITH STREPTOCOCCUS VACCINES. CLIFFORD L. DERICK and JAMES P. O'HARE, New England J. Med. **208**:578 (March 16) 1933.

Sixty-seven patients with nephritis were subjected to skin test with nucleoprotein extracts of streptococci; both the incidence and the intensity of the reaction to the hemolytic streptococcus nucleoprotein were usually greater than to the green variety of streptococcus. Reactions were obtained in 83.5 per cent of six cases of acute hemorrhagic nephritis, in 74 per cent of thirty-one cases of sub-

acute hemorrhagic nephritis, in 32 per cent of twenty-two cases of chronic hemorrhagic nephritis and in 50 per cent of eight cases with the syndrome of nephrosis.

Intravenous vaccination with the purified nucleoprotein fraction of streptococci was tried in twenty patients from 10 to 45 years of age with acute or subacute hemorrhagic nephritis. In each case the type of streptococcus nucleoprotein to which they were most sensitive was used. In eleven instances this was the hemolytic variety, and in only one of the eleven the desensitization could not be completed. In eight of the cases, desensitization has persisted in periods up to thirty-three months from the time of vaccination. In one patient sensitive to the homologous nucleoprotein and in one sensitive to the heterologous variety there were mild recurrences.

In two patients who were about equally sensitive to both varieties of nucleoprotein, a mixture of equal amounts was used. Complete desensitization was obtained and has persisted two and nine months.

Of seven patients more sensitive to the green variety of streptococcus, two were completely desensitized and remained so; two showed a persistence of mild hypersensitiveness; one has become more sensitive to both varieties, and in one it was not possible to make a skin test at the completion of the treatment.

Clinically, the three patients with acute hemorrhagic nephritis did very well, and the condition of thirteen of the remaining seventeen has either improved or remained unchanged after an interval as long as thirty-five months; in one patient chronic hemorrhagic nephritis has definitely developed and the condition in the other three patients has apparently progressed unfavorably.

GENGENBACH, Denver.

THE COMPARATIVE VALUE OF THE SCRATCH AND INTRADERMAL METHODS OF SKIN TESTING IN ASTHMA AND HAY FEVER OF CHILDREN. EDWARD S. O'KEEFE and LEO B. BURGIN, New England J. Med. **208**:582 (March 16) 1933.

The group studied was composed of children under 12 years of age. Twenty-two of the children had hay fever and seventy-one had asthma.

The scratch tests were performed on the forearm, a 1:100 solution of the antigen prepared according to Coca's method being used. The intradermal tests were done on the outer aspect of the upper arm with a 1:1,000 solution of the antigen, also prepared according to Coca's method. In the intradermal tests, 0.02 cc. was injected intradermally, and the readings were made in from fifteen to twenty minutes. An injection of the solvent was made in each case, and was used as a control. Any wheal or erythema which was definitely larger than the control was considered positive. The pollens chosen were red top, orchard grass, timothy and ragweed. Of the ninety-three children tested, forty-two (45 per cent) gave a positive reaction to the scratch test but were not tested intradermally. Forty (43 per cent) gave a negative reaction to the scratch test and a positive reaction to the intradermal test. Eleven gave a negative reaction by both methods. Of the entire group 88 per cent gave a positive reaction.

Of the twenty-two children with hay fever, twenty gave a positive reaction and only two a negative reaction to the scratch test. These two gave a positive reaction to the intradermal test. Of the seventy-one children with asthma, twenty-two gave a positive reaction to the scratch test; of the remaining forty-nine children, thirty-eight gave a positive reaction to the intradermal test, and eleven gave a negative reaction to both tests.

Thus 100 per cent of the children with hay fever gave a positive reaction, over 90 per cent reacting positively to the scratch test.

Among the asthmatic children, the scratch test from pollens was positive in only 30 per cent, whereas this increased to 87 per cent when the intradermal method was used.

Of twenty-two children who had pollen asthma with a definite exacerbation of symptoms during the pollen season, sixteen, or 63 per cent, showed a negative skin test and a positive intradermal test and six, or 27 per cent, showed a positive scratch test.

The use of the intradermal test in this group increased the percentage of positive tests from 27 per cent, as given by the scratch method, to 90 per cent.

The scratch test is reliable in the hay fever of children, but in the asthma of children it should be followed by the intradermal test in all cases in which the scratch test is negative.

GENGENBACH, Denver.

A BRIEF REVIEW OF THE ESSENTIAL PATHOLOGY OF PERICARDITIS. CHARLES F. BRANCH, New England J. Med. **208**:771 (April 13) 1933.

Acute pericarditis is almost always of bacterial origin. The pneumococcus is responsible for about 35 per cent of the cases and the organism of rheumatic fever for about 30 per cent, while other organisms such as staphylococci, streptococci and the tubercle bacillus account for about 15 per cent. The remaining 20 per cent of the cases of acute pericarditis are noninfectious and occur as the terminal event in such diseases as uremia, diabetes, the profound anemias and leukemias and coronary thrombosis.

Acute pericarditis shows a striking incidence in males as compared with females, the ratio being 3:1, and it has been reported in persons aged from 1 to 75 years, with an average age of 35. Negroes are more susceptible to the disease than white people.

It is much more common than not to find a simple serous inflammation developing into a serofibrinous condition or even becoming fibropurulent in character.

The normal amount of pericardial fluid varies from 25 to 50 cc., and the usual abnormal amount present is less than 500 cc., although over 4,000 cc. has been reported. Because this fluid accumulates gradually and rarely in large quantities, cardiac embarrassment is unusual.

Serious complications arise when adhesions firmly fix the visceral and the parietal pericardium to each other or to the pleura, the diaphragm or the mediastinum, so that definite limitation of motion increases the work of the heart, thereby affecting both its size and its function.

Hemorrhagic pericarditis should invariably refer to an acute inflammatory reaction. It is most characteristically found as an accompaniment of tuberculosis, syphilis, malignancy of the pericardium or coronary thrombosis.

Tuberculous pericarditis, though not common, is far from rare. It is, of course, secondary to tuberculosis elsewhere, and almost invariably is a direct extension from the pleura or the mediastinal lymph nodes.

GENGENBACH, Denver.

MEDICAL ASPECTS OF PERICARDITIS. S. A. LEVINE, New England J. Med. **208**:773 (April 13) 1933.

The author presents the following clinical classifications:

1. Hydropericardium. This is similar to hydrothorax. Treatment is directed at the cause of the condition. Tapping is of little value.

2. Adhesive pericarditis, adherent pericardium. This is often not diagnosed until postmortem examination. Fixation of the apex impulse, Broadbent's sign and polyserositis are helpful but not wholly reliable signs.

3. Acute nonrheumatic pericarditis. This occurs in from 10 to 20 per cent of cases of coronary thrombosis.

4. Tuberculous pericarditis. This is a very serious condition, with a high mortality.

5. Rheumatic pericarditis. When this condition arises, it is apt to develop several weeks after rheumatic fever. No new therapy is needed, except possibly a locally applied icebag.

6. Metastatic pericarditis. This is a purulent type of pericarditis, most common in children after infections of the upper respiratory tract. Drainage is necessary and life-saving.

GENGENBACH, Denver.

FAMILIAL HEPATOMEGALY OF UNCERTAIN PATHOLOGY. E. BELLINGHAM SMITH and ELIZABETH O'FLYNN, Lancet **1**:297 (Feb. 11) 1933.

A boy, aged 6, was admitted to the hospital with cough, breathlessness and abdominal pain. The mother had first noticed enlargement of the abdomen when the child was 1 year and 3 months of age; since then he had been almost constantly in hospitals. A diagnosis of Gaucher's disease was made on the recovery of tissue pulp containing large clear cells from what was thought to be a splenic puncture but which in reality was a puncture of an enormously enlarged left lobe of the liver. The boy was undersized and had an abnormally large head and a fat face. The skin of the face, trunk and limbs was pigmented a deep brown; that of the hands and feet was ashy gray. There was some clubbing of the fingers, but this could be explained by the presence of advanced fibrosis and bronchiectasis affecting the lower lobes of both lungs. Large quantities of fetid sputum were expectorated. The abdomen was prominent and hard. The liver was greatly enlarged, extending to the iliac crest on the right side and passing obliquely upward on the left, merging with what was thought to be a large spleen.

At autopsy a liver weighing 2,500 Gm. and almost filling the abdominal cavity was found. The most striking features of the microscopic examination of sections of the liver were: (1) the emptiness of the individual cells; (2) their increase in size, sometimes to two or three times the normal size; (3) the preservation of the nucleus in most cells; (4) the increase in connective tissue in the region of the portal spaces, and (5) the arrangement of the cells in groups of from four to twenty.

A case somewhat similar to this has been described by von Gierke under the title "Hepato-Nephromegalia glykogenica."

LANGMANN, New York.

SERUM DISEASE. W. MIKULOWSKI, Arch. de méd d. enf. **36**:161 (March) 1933.

Although credit for grouping certain phenomena following the injection of foreign protein under the term serum sickness properly belongs to Pirquet and Schick, it is a matter of medical record that, as early as 1891, Ricket and Hericourt called attention to the local pain and pruritus following injections of serum for tuberculosis. Roux and Martin observed articular swellings, while others have noted the syndrome comprising pain in the joints and fever, simulating a rheumatic crisis.

In the articular response, as contrasted with that of the skin, for example, the dominating characteristic symptom is pain, unaccompanied, as a rule, by heat, redness or swelling. A singular development in the study of these reactions is the observation in certain cases that the resorption of the patient's own protein, uninfluenced by the injection of foreign albumin, may produce an identical physiopathologic picture.

Mikulowski presents the case histories of three children, aged 3, 9 and 8, respectively, to illustrate the failure, probably on the part of the liver, to assist in the normal digestion of albumin. These children were suffering from tuberculous invasion of the serous cavities, and the symptomatology could well be described under the term proteinic arthropathy of Bezançon.

AMESSE, Denver.

STILL'S DISEASE BEGINNING IN THE CERVICAL SPINE. DEBRÉ, BROCA and CRÉMIEUX, Bull. Soc. de pédiat. de Paris **30**:234 (April 19) 1932.

A girl, aged 3½ years, had the signs typical of Still's disease. The onset was particularly interesting, as the cervical vertebral joints were involved. This suggested Pott's disease, but a negative reaction to the tuberculin test, roentgenograms which showed repeatedly negative findings so far as any bony involvement was concerned and the subsequent development of chronic arthritis of many other joints confirmed the diagnosis of Still's disease.

BENJAMIN, Montreal, Canada.

PERIOSTEAL DYSPLASIA. A. D. RADULESCO and B. SUSAN, Rev. d'orthop. **20**:5 (Jan.-Feb.) 1933.

Periosteal dysplasia is an osteodystrophia which is rarely seen in the clinic. The etiology and pathology are indefinite though the condition has been described under a multitude of names.

In order to bring out their theory, the authors discuss the histology and embryology of bone. Briefly, bone, cartilage, ligaments, blood vessels and aponeuroses are of mesenchymal origin. The growth of bone occurs by ossification of the enchondral cartilage through a process of calcification of the diaphyso-epiphyseal cartilage.

Periosteal dysplasia is a systemic disease affecting all tissues of mesenchymal origin. It may manifest itself during intra-uterine life (congenital form) or postnatally. Males are affected more frequently than females, and persons living in northern Europe are affected more commonly than those living in southern Europe. Griffith reported a hereditary factor in 15 per cent of the cases he observed. Several authors have reported a history of the disease in several generations of a family. Cure occurs spontaneously when adult life is reached (the end of mesenchymal activity), though few persons affected reach this age. The outstanding symptom is excessive fragility of the bones. Multiple fractures occur with little or no cause. Such fractures may occur during intra-uterine life or postnatally.

*Intra-Uterine Type.*—In this form the child is of the micromegalic type, myxedema is absent, premature birth is the rule, and the fetus is most frequently stillborn. If the child is delivered alive, death usually occurs soon after delivery. On examination of the body, multiple fractures are found.

A subtype of the intra-uterine form is occasionally seen, the "tardive" form. This type occurs in children who have the intra-uterine form of the disease but who live. The head is small, the hair is excessive, subcutaneous tissue is abundant, the face is slender, almost wretched in appearance, and the chin is prominent. The eyes are noteworthy for the blue scleras, the body is long and larger than normal, and rachitic nodules are felt along the costal margins. The abdomen is distended. There frequently are associated malformations, such as clubfoot or hernias. The skeleton is incompletely ossified. Multiple fractures of the legs, arms or ribs may be present, or old fractures, healed or partly healed, may be observed. Secondary deformity is common.

*Postnatal Type.*—Grossly, these children appear normal at birth, except that the scleras are bluish. The first fracture may occur at any age. Flemming reported that he saw a child with such a fracture at 18 months of age. The fractures occur with but slight trauma, and, while some pain is felt at the site of the fracture, this is much less than would normally occur. Little or no displacement of the fragments is the rule, and the periosteum does not appear to be torn; i. e., the fractures are subperiosteal. The site of fracture is almost always in the diaphysis and rarely in the epiphysis of the bone. Healing is rapid. Occasionally ankylosis complicates the picture. The number of fractures diminishes as the child grows older, and the fractures cease when adult life is reached. The more delayed the appearance of the first fracture, the less numerous are the fractures. As many as 250 fractures have been observed in one child.

Pathologically, there is decalcification of the long bones, the medullary cavity is larger than normal, and the cortex is thin and almost transparent. The periosteum is usually thick, and small hemorrhagic areas appear in it. The medulla has a pseudocystic appearance at times. The vertebrae are cartilaginous, ossification is deficient, and the total length of the column is shorter than normal. The body structure of the ears shows hyperplasia of the labyrinth, ossification is diminished, and the small bones are more fragile than usual. Sclerotic changes are frequently seen in the aorta. The glandular structures show premature development. This is especially marked in the thyroid, parathyroid, suprarenal and thymic tissues. At the site of the fractures the periosteum is increased in

thickness, and the subperiosteal tissue is partly transformed into bone, giving the appearance of granular calcification. All tissues of mesenchymal origin show modifications in structure, as those of the viscera.

*Diagnosis.*—In the differential diagnosis one must consider congenital arthrosis, achondroplasia, dyschondrosteosis and fetal rickets. In addition, the postnatal form must be differentiated from osteosarcoma, gumma, echinococcic cyst, Recklinghausen's disease and infantile osteomalacia.

*Treatment.*—Little success has been obtained with various methods of treatment. Cod liver oil or cod liver oil with calcium has been of benefit in a few cases. Thyroid therapy may have a beneficial effect. Actinotherapy has also been tried, with occasional success.

RYAN, Vancouver, Canada.

SEDIMENTATION TEST AS A GUIDE IN THE TREATMENT OF RHEUMATISM AND HEART DISEASE IN CHILDHOOD. GERHARD STELLER, Kinderärztl. Praxis **3**:338 (Aug.) 1932.

The sedimentation test of the blood is a valuable guide in determining the length of time active treatment should be continued in cases of rheumatism and of cardiac disorders. As an index of the activity of rheumatic conditions it is better than the range of temperature or the persistence of rheumatic pains. It should help to decide the amount of time indicated for rest in bed.

HUENEKENS, Minneapolis.

PROGNOSIS OF RHEUMATIC HEART DISEASE. EDMUND NOBEL, Kinderärztl. Praxis **3**:347 (Aug.) 1932.

Seventy-eight patients suffering from some form of rheumatic disease were reexamined after a period of from five and one-half to eighteen and one-half years. Nine patients had erythema nodosum; forty-two, acute rheumatic arthritis; twenty-one, chorea rheumatica, and six, both chorea and articular rheumatism. On reexamination, 42.8 per cent of the patients who had arthritis, 47.5 per cent of those who had chorea and 66.6 per cent of those who had erythema nodosum showed no involvement of the heart. All the children in whom chorea and articular rheumatism were combined had heart disease.

HUENEKENS, Minneapolis.

GOITER, GOITER HEART AND IODINE SENSITIVITY IN INFANTS. FRANZ LUST, Kinderärztl. Praxis **3**:441 (Oct.) 1932.

Even the normal thyroid gland of the new-born infant varies greatly in weight, depending on whether or not the child is born in a locality where goiter is prevalent. The average weight of the thyroid gland of the new-born in Bern is 8.2 Gm.; in Munich, 6 Gm.; in Königsberg, 3.5 Gm., and in Kiel, 1.9 Gm. The author reports thirteen cases of congenital struma with severe symptoms.

Diagnosis is made by palpation and by noting the relief from cyanosis and dyspnea obtained when the head is pushed backward. Treatment consists in keeping the head bent backward, plus the administration of a single dose of 0.1 mg. of potassium iodide; the swelling usually subsides in four or five days. In many cases enlargement of the thyroid is accompanied by enlargement of the heart. Feer found that in normal new-born infants the transverse diameter of the lungs divided by the transverse diameter of the heart gave an average quotient of 1.87. In new-born infants with goiter and enlargement of the heart this quotient averages 1.63. The average diameter of the enlarged hearts is 5.8 cm., which is not attained in normal infants until the fourth month. The cardiac enlargement is caused by hypertrophy and dilatation, and the heart becomes smaller in a few days if iodine is given. The new-born infant is unquestionably sensitive to iodine, and there are many arguments for and against its use in cases of congenital struma.

HUENEKENS, Minneapolis.

ADOLESCENT PSEUDOMASTITIS. LUDWIG F. MEYER, Kinderärztl. Praxis **3**:489 (Oct.) 1932.

The author calls attention anew to the painful mammary swelling in young people of both sexes, occurring between the ages of from 10 to 12 years in girls and from 14 to 16 years in boys. The condition is probably due to hormonal activity, especially that of the anterior lobe of the hypophysis. Treatment is unnecessary and is of little avail.

HUENEKENS, Minneapolis.

PATHOGENESIS OF PNEUMONIA IN CHILDHOOD. A. J. STRUKOW, Monatschr. f. Kinderh. **57**:81 1933.

On the basis of histologic studies, the author concludes that in addition to immunobiologic factors the morphologic structure of the child's lungs predisposes to the development of pneumonia. The tissues are more loosely bound, the openings into the acini are larger and the lymph spaces are much wider than in the lungs of the adult. Strukow presents microscopic photographs demonstrating the enlarged lymph spaces. On the basis of his studies he concludes that pneumonia is primarily an involvement of the lymphatics. The first involvement occurs around the peribronchiolar tissue, causing stagnation of the circulation of the lymph. This predisposes to further infection, which travels rapidly along the lymphatics to the hilus. As it progresses toward the hilus, the larger bronchioles become involved, with resulting stagnation in other radiating lymph channels and a spread of the process. The invariable enlargement of the hilar lymph nodes is evidence in favor of this hypothesis.

GERSTLEY, Chicago.

PNEUMONIA ASSOCIATED WITH JAUNDICE. VILMA SZARKA, Monatschr. f. Kinderh. **57**:90, 1933.

Jaundice occurs rarely in conjunction with pneumonia; it was seen only five times in nine hundred cases studied by Szarka. The prognosis is not necessarily grave, as three of the patients recovered. The etiology is uncertain; it is not dependent on an increased destruction of erythrocytes, but is probably associated with faulty function of the liver.

GERSTLEY, Chicago.

DISTURBANCES OF THE DIGESTIVE TRACT IN EARLY CHILDHOOD. MARTIN JACHENS, Monatschr. f. Kinderh. **57**:100, 1933.

The article contains case reports and seven x-ray pictures and diagrams of atresia of the esophagus, duodenal stenosis and stenosis of the large intestine.

GERSTLEY, Chicago.

TRANSFUSION OF CITRATED BLOOD. EDUARD HACKER and G. GARCIA OLIVER, Monatschr. f. Kinderh. **57**:113, 1933.

The authors review the subject of the transfusion of blood. They used the citrate method in a variety of conditions. Favorable results are reported in cases of bleeding from hemophilia and in secondary anemia, but they are not optimistic as to the benefits of this method in cases of acute sepsis and in those of most diseases of the blood-forming organs. No benefit was obtained in cases of pneumonia or in those of malignant diphtheria. In spite of the criticism of the method by other authors, Hacker and Oliver recommend it because of the simplicity of its technic.

GERSTLEY, Chicago.

UROBILIN METABOLISM IN CHILDREN. W. BIRK, Monatschr. f. Kinderh. **57**: 169, 1933.

The metabolism of urobilin is not well understood because of the unreliability of experimental procedures. For instance, it is excreted both in the stool and in the urine. In the intestine putrefactive bacteria reduce bile pigments to urobilin-

ogen. Hence in putrefactive conditions much urobilin is found. If fermentation predominates, no urobilin appears in the stool.

In spite of these difficulties, Birk made determinations of the excreted urobilin in cases of acute and chronic leukemia, of purpura and hemorrhagic disease, of catarrhal jaundice, of thrombosis of the splenic veins and of anemia. He was forced to conclude that these studies have little clinical value. Apparently most of the urobilin in the intestine is reabsorbed in the body and that which remains in the excretion is of slight clinical importance.

GERSTLEY, Chicago.

A NEW TREATMENT FOR NOCTURNAL ENURESIS. N. J. KRASNOGORSKI, Monatschr. f. Kinderh. **57**:252, 1933.

The author recommends a simple procedure which he has found satisfactory during the last three years. The idea is based on a series of observations started by Gantt in 1927. His first studies on salivary secretion showed that this is diminished following a restricted intake of fluid. A year later Harbedia found that there was no decrease in salivary secretion following dehydration of the patient from excessive perspiration. Evidently in his experiments there had been a reserve of water in the body.

When Krasnogorski reviewed Gantt's experiments he found that the children studied had had salt ham and herring for breakfast. Evidently the diminution of salivary secretion resulted not from the restriction of fluid, but from the salty food. Control experiments with ordinary sodium chloride confirmed this idea. Similar experiments on dogs showed a diminution in pancreatic secretion following the ingestion of as little as 5 Gm. of salt.

The treatment suggested for enuresis, based on these experiments, is to allow the patient plenty of fluids—water, milk and soup—in the first half of the day. No fluid is allowed after 4 p. m. At 6 p. m. supper is offered, consisting of foods low in water (bread, butter, eggs, meat and fish, but no vegetables, fruit or cereals). No salt is allowed. Under these conditions the day's intake of water is excreted by 8 p. m. At 8:30, when the child is already sleepy and in bed, he receives salt in the form of buttered bread with ham, herring or caviar (approximately 5 Gm. of salt). This amount is sufficient to cause retention of water through the night, with little inconvenience to the child. The 100 to 125 cc. of urine secreted during the night is insufficient to start the reflex of emptying the bladder.

GERSTLEY, Chicago.

GEOGRAPHIC TONGUE. RICHARD WEIGERT, Monatschr. f. Kinderh. **57**:306, 1933.

Geographic tongue does not appear in the first two months of life. It occurs for the first time most frequently in the second and third quarters of the first year and then more infrequently until the thirtieth month. When associated with exudative diathesis, it occurs as a first symptom in 25 per cent of cases.

GERSTLEY, Chicago.

UNUSUAL AORTIC LESION IN A NURSLING. K. WOLFF, Virchows Arch. f. path. Anat. **285**:369, 1932.

An infant who died on the twelfth day after birth presented during life the following syndrome: malformation of the right ear, cloudiness of the cornea, cyanosis and a greatly enlarged heart. The antemortem diagnosis was congenital malformation of the heart. The Wassermann reaction of the infant and that of the mother were negative, and gross and histologic examination revealed no evidence of syphilis. At necropsy the heart was found to be enlarged but devoid of developmental errors. In the ascending, transverse and descending portions of the aorta were seen narrow, cleftlike areas that had the appearance of tears. The lesions ceased abruptly just below the diaphragm. Microscopic examination revealed as the earliest lesions poorly defined, irregular areas in the media, in

which the elastic fibrils had disappeared. The collagen fibers were swollen and had also in part lost their identity. Muscle tissue was apparently the last element to be altered; the areas contained muscle nuclei in various stages of degeneration. The ground substance had the staining reaction of mucoid degeneration. The surface of the intima was intact over the lesions. Most striking was the absence of any reparative or cellular infiltrated reaction of the tissues in or about the lesions. In the macroscopic tearlike lesions also, reactive phenomena were entirely wanting. The material resulting from the degeneration of the elastic and other tissues of the media had apparently been absorbed, and the intact intima had been folded into the defect thus produced. The small vessels were normal. The lesion described is most like that which Erdheim has described in the aorta of elderly persons as the cause of spontaneous rupture of the aorta, but which has not hitherto been seen in the earlier periods of life. In the case described no cause for the lesion could be found. SCHULTZ, Evanston, Ill. [ARCH. PATH.]

AMYLOIDOSIS IN A NURSLING. I. OBERG, Virchows Arch. f. path. Anat. **286**:476, 1932.

Amyloidosis is rare in infancy. With the exception of one doubtful case in a child, aged 1½ years, the author could find no reference to the occurrence of the condition in children under 4 years of age. The case reported was that of a child, aged 2½ months, who died after pneumococcic meningitis secondary to bilateral otitis media. The gross appearance of the spleen led to an anatomic diagnosis of amyloid disease. The splenic pulp and the glomeruli of the kidney on microscopic examination contained protein material with the optical and physical properties and the localization of amyloid. The material did not give the characteristic microchemical reactions of amyloid.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

A CASE OF CHOLESTEROL PERITONITIS. T. SATO, M. YAMAGISHI and J. ASANO, J. Pediat. (Tokyo), no. 386, p. 1355, July 20, 1932.

The authors report a case of what they call "cholesterol peritonitis," which was so diagnosed because of the negative tuberculin and Wassermann tests and a slightly increased amount of cholesterol in the peritoneal fluid. The quantitative determinations of the cholesterol content of the blood and of the peritoneal fluid from this patient (a boy, 4 years and 8 months of age), the micromethod of Yoshimatsu being employed, are tabulated as follows:

| Date | Blood Cholesterol | Cholesterol in Peritoneal Fluid |
|---|---|---|
| 4–23 | 250.0 | 330.0 |
| 5– 6 | ..... | 245.2 |
| 5–16 | 230.4 | 207.5 |
| 6–12 | 225.8 | ..... |

The average values for cholesterol are not very high, although the authors observed the presence of doubly refractile lipoids as well as the cholesterol crystals in the peritoneal fluid with the polarizing microscope. The patient finally recovered.

KATO, Chicago.

LAWRENCE-BIEDL DISEASE. J. J. WUITE, Nederl. tijdschr. v. geneesk. **76**:1108 (March 5) 1932.

A case of Lawrence-Biedl disease with not only the classic symptoms, such as accumulation of fat and genital atrophy, but also retinitis pigmentosa, polydactylism and choreic-athetoid movements was seen; the last symptom, a result of the involvement of the corpus striatum, gives a hint that Biedl and Raab's theory, that the adipositas is of diencephalic and not of hypophyseal origin, is true.

VAN CREVELD, Amsterdam, The Netherlands.

ATYPICAL CHRONIC MYELOID LEUKEMIA WITH CUTANEOUS MANIFESTATIONS OF AN APPARENTLY INFLAMMATORY CHARACTER. C. J. GELDERMAN, Nederl. tijdschr. v. geneesk. **76**:1593 (April 2) 1932.

The author describes a case of chronic myeloid leukemia with a typical clinical development in a girl aged 10 years. There are intervals of apparently good health and, perhaps, a normal blood picture. Exacerbations occur in the form of an acute myeloblastic leukemia, without mucosal symptoms or hemorrhagic diatheses and with passing violent cutaneous manifestations in the form of apparently phlegmonous cutaneous infiltrations. Remissions from the exacerbations occur spontaneously.

VAN CREVELD, Amsterdam, The Netherlands.

OBSTIPATION IN CHILDREN. L. DE JAGER, Nederl. tijdschr. v. geneesk. **76**:3178 (June 25) 1932.

The author's long experience in treating obstipation in children (not babies) has taught him that the principal remedy is to get the children accustomed to defecate at regular intervals. In severe cases, however, he gives one porridge-spoonful of a potion of 25 Gm. of sulphate of magnesium three or four times a day for about ten days until 200 Gm. has been given; the results are excellent, especially in cases in which the obstipation is caused by laziness, love of ease or fear and in which the peristalsis of the intestines is sufficient.

VAN CREVELD, Amsterdam, The Netherlands.

PYLORISTENOSIS AND NEUROPATHY. E. J. M. BELINFANTE, Nederl. tijdschr. v. geneesk. **76**:3727 (July 30) 1932.

As a control, examinations were made of thirty-two children who as babies had shown symptoms of pyloristenosis. It appeared that these children had more symptoms of neuropathy than other children of the same age examined at the same time. This result is in accordance with the impression that a nervous predisposition plays a rôle in the production of this condition. Contrary to the observations made in the cases in the literature, hypertrophy of the pylorus was not found in one child who died several months later from an intercurrent disease.

VAN CREVELD, Amsterdam, The Netherlands.

LARYNGOSTENOSIS AND "STENOSIS WEATHER." P. H. KRAMER, Nederl. tijdschr. v. geneesk. **76**:3834 (Aug. 6) 1932.

A characteristic case of primary diphtheritic laryngostenosis is described. The patient was one of a group of five patients with laryngostenosis who were taken to the hospital within twenty-two hours. In 1931, also, a group of four cases of laryngostenosis occurred twice in four days. In these three groups, the metereologic circumstances corresponded with the so-called "stenosis weather;" when periods of low barometric pressure are interrupted by a short period of high pressure, probably a peculiar influence is exercised on the inflamed larynx, which may give rise to the symptoms of stenosis.

VAN CREVELD, Amsterdam, The Netherlands.

INTESTINAL INFANTILISM AND ITS TREATMENT WITH A PREPARATION OF DRIED HOG STOMACH. H. A. STHEEMAN, Nederl. tijdschr. v. geneesk. **76**:4823 (Oct. 15) 1932.

The author first gives a short survey of the typical symptoms in Herter's disease and of the explanation given for these symptoms. He is of the opinion that the pancreatic origin of the clinical picture is possible, and he bases his opinion on two observations of his own. He gives a report of four cases of celiac disease in children. Two children presented the symptoms of the type of Herter; another child gave the type of Heubner, and the fourth showed the symptoms of Indian sprue, though devoid of Hunter's tongue and without infantilism. This last

case was of a particularly serious character. The impossibility of finding an efficacious dietary was the outstanding feature in all cases. For months, and even years, chemical and dietetic treatment had been without success. An immediate improvement set in when a preparation of dried hogs' stomachs in a daily dose of 10 Gm. was administered with the same diet, with which therapy had previously failed. Vomiting, anorexia, fatty stool, diarrhea, general atrophy, psychic depression, delay of growth and an abnormally high index for the hemoglobin disappeared. Total recovery followed in less than three months. In three of the patients, a relapse has not been seen within half a year after discharge. Their physical appearance was excellent.

VAN CREVELD, Amsterdam, The Netherlands.

## Nervous Diseases

NATURE OF FEEBLE-MINDEDNESS. ABRAHAM MYERSON, Am. J. Psychiat. **12**:1205 (May) 1933.

The term feebleminded implies an intelligence so low as to be declared pathologic. This paper represents a study of feebleminded subjects, many of whom reside at the Walter E. Fernald School in Massachusetts. These persons were divided into groups thus: (1) cretins, (2) mongolian imbeciles, (3) organic types (with tremors, paralysis, etc.), (4) microcephalic persons, (5) those with congenital syphilis, (6) unclassified or unknown feebleminded persons (those who usually remain in the community). The sixth group presents the greatest problem, "and it is concerning this group that we have the least knowledge."

The first four groups, contrary to popular belief, cannot be linked scientifically with inheritance. A study of fifty-nine patients with congenital syphilis together with a review of the literature on the subject brings the author to the following conclusions: (*a*) In institutions for the feebleminded the percentage of children with congenital syphilis is only slightly, if at all, greater than that of nonsyphilitic children. (*b*) Direct evidence of involvement of the brain in congenital syphilis is scanty. (*c*) A large proportion of this group comes from families in which there is much feeblemindedness. In other words, if there is a hereditary element in feeblemindedness, it may be held responsible for a large proportion of the cases labeled congenital syphilitic feeblemindedness. (*d*) The social stratum in which the parents of these feebleminded persons live is conducive to a large percentage of cases of syphilis. (*e*) Syphilis may cause alterations in the brain producing dementia, but dementia is not feeblemindedness.

In the unclassified group, the feebleminded are also definitely feeble-bodied. There is not only an appalling incidence of poor nutrition, bad teeth, diseased tonsils and defective hearts, but also a high frequency of developmental defects: skeletal anomalies, defective ears, palates, etc. As to hereditary phenomena associated with feeblemindedness, the author is inclined to the belief that environmental influences (factory work, crowded quarters, undernutrition, infections, etc.) on the germ plasm are more likely factors than the mendelian laws. JAHR, Omaha.

BLOOD CHOLESTEROL STUDIES IN MENTAL DISEASE: II. SCHIZOPHRENIA. PURCELL G. SCHUBA, Am. J. Psychiat. **12**:1227 (May) 1933.

Though some schizophrenic patients may show a normal or somewhat increased amount of cholesterol in the blood, there is a definite tendency to a lowered blood cholesterol in this group. Fifty-five cases were studied. While the normal blood cholesterol ranges between 110 and 195 mg. per hundred cubic centimeters, the findings in this group ranged from 50 to 300 mg., with a definite concentration of cases in the lower half and a prominent paucity of cases in the upper half.

JAHR, Omaha.

SCHIZOPHRENIA IN CHILDREN. HOWARD W. POTTER, Am. J. Psychiat. **12**:1254 (May) 1933.

Deviations of thinking, feeling and acting are different in children than in adults because the central nervous system is in a developmental stage. Consequently the child is unable to respond with the complexity of the adult in functional expression, since his experience and intellectual development are limited. In this paper schizophrenia is limited to the following reaction types: (1) a generalized retraction of interests from the surroundings; (2) dereistic thinking, feeling and acting; (3) disturbances of thought manifested through blocking, symbolization, condensation, incoherence and diminution, sometimes to the extent of mutism; (4) defective emotional rapport; (5) diminution, rigidity and affective distortion; (6) alterations in behavior with an increase in motility leading to incessant activity or a diminution of motility leading to complete immobility or stereotypy. Psychodynamically, regression is characteristic. The author gives a brief review of the literature on the subject, as well as the reports of six cases.

JAHR, Omaha.

SOCIABILITY OF ABNORMAL CHILDREN AND SOCIAL CHILD PSYCHOLOGY: SOCIABILITY AS A MENTAL TEST OF CHILD GROUPS. F. SCHNEERSOHN, Am. J. Psychiat. **12**:1307 (May) 1903.

Social child psychology concerns itself with the mental group life of the child in his concrete entity and his peculiarity. There are three forms of collectives operating: (1) the family, (2) the locale or neighborhood and (3) the school. Each of these has a different structure, and each in turn has its significance in its social influence on the child. The family collective consists of the child's brothers and sisters whose ages are close enough for the formation of a play group. The children have common hereditary qualities and blood relationships. Here are formed warm attachments, experiences and memories. The children share the common home life, the innumerable incidents in the home milieu. The child learns relationships to those about him. The only child is handicapped in this respect and must compensate for this training in later years. The local collective consists of the children from one building, one yard or one street. These share common interests incident to proximity. The outdoors with its open and hidden charms awakens in the child deep instincts and emotions which are expressed in common games. These games are of special significance in the study of child group life. The school collective belongs to a higher order. Here the collective is divided into different groups (age and mental ability). This collective unites the children for a number of years, and often the fate of the child's future is in this collective.

This paper deals with a study of social behavior of a group of children with different mentality ranges in Randall's Island. The observations are made with particular emphasis on the children in social relation to one another. The imbecile collective is characterized by immobile silence, isolation and playlessness. Some members show automatic movements (self-play). The less retarded children show a somewhat higher stage of sociability. Here the whole group moves, stimulating and imitating one another. The group forms and dissolves continuously. The moves are chaotic and the playing is structureless. Generally, the higher the intellectual level of the collective, the more organized is the group and the more definite are the structure and content of the play (games). Sociability may therefore serve as a mental test for the collective, the criteria being movements, communication, group formation and games. Sociability is also a certain intelligence test for the individual child as well as a decisive factor in his emotional life. In the case of the nervous child sociability may be a cause or a condition of his emotional status.

In the treatment of sociability the investigation shows that even in the very limited contacts there are "traces" of a higher stage. On the general background of silence and isolation a momentary reaction of sociability in the collective may be flashed. These "traces" or "outbursts" have a clinical significance for educational possibilities through careful training and guidance. The author considers the play theory in terms of "psychic vitamins" thus: "Just as the 'useful' work

satisfies the concrete needs of the struggle for existence, so the 'useless' play is of vital importance, as it stimulates the urge to the life struggle and sustains the tonus of mental life." The asocial nervous child may suffer from psychic scurvy.

A comprehensive discussion on the biology of play and its significance is included in this thorough study of the subject. A scheme for investigation of group life of the child is appended.

JAHR, Omaha.

THE SIGNIFICANCE OF THE COMPLAINT FACTOR IN CHILD PSYCHIATRY. LEO KANNER, Am. J. Psychiat. **13**:171 (July) 1933.

A translation of the patient's (or parent's) complaint into the examiner's abbreviated terminology causes, in many instances, a loss of highly important points that offer insight into an already complicated problem. The uninterrupted recitation of an oversolicitous complainant frequently illuminates a family secret which may be the underlying cause of the existing trouble, and unless the report is recorded verbatim the essential picture of the child's constellation is missed. In relating the complaint a verbose mother frequently and innocently describes a vivid picture characterizing the environment which influences and is influenced by the patient. Incidental remarks often reflect eloquently the parental attitudes and expectations, prevailing superstitions and popular lore and may be utilized in unearthing mysterious bases for physical complaints as well as bizarre causes for psychogenic ills. The complaints are grouped according to the following reaction patterns: (*a*) personality difficulties following physical illness, a lesion of the brain with its sequelae — congenital, acquired or dysfunctional — Sydenham's chorea and endocrinopathies; (*b*) difficulties due to involuntary partial dysfunction of the central nervous system, digestive systems, circulatory systems, etc.; (*c*) difficulties including the person as a whole; these include intellectual inadequacy, emotional disturbances, difficulties in thought, disorders of speech, habitual manipulations of the body (tics), faulty feeding habits, disturbances of sleep, antisocial trends, sexual difficulties, attack disorders, minor psychoses, major psychoses and suicide.

JAHR, Omaha.

MONGOLOID IDIOCY IN A NEGRO INFANT. JOHN E. DUNLAP, J. Pediat. **2**:615 (May) 1933.

The typical findings of mongolian idiocy were observed in a Negro boy, aged 7 months. The parents were not full-blooded Negroes.

LEMASTER, Evanston, Ill.

EPILEPSY AND DEHYDRATION. D. M. LYON and D. M. DUNLOP, Edinburgh M. J. **40**:266 (May) 1933.

Recently there has been some advance toward a knowledge of the etiology of epilepsy. The authors attempted to repeat in adult epileptic patients the observations made by McQuarrie and by Peiler; also to study the effect of alkalis in increasing the seizures and to reverse the process so as to curtail the frequency of the attacks.

The writers were able to produce major seizures in adult epileptic patients by forcing an intake of fluids and inhibiting diuresis by means of solution of pituitary. Alkalis cause fits to recur more frequently. An acidosis occurs during the convulsion. Dehydration acted therapeutically in almost every case, causing an improvement which seemed as marked as that following the use of a ketogenic diet. Phenobarbital gives the best results, which are enhanced by persistent dehydration.

NEFF, Kansas City, Mo.

A Form of Progressive Cerebral Sclerosis in Infants Associated with Primary Degeneration of the Intrafascicular Glia. J. G. Greenfield, J. Neurol. & Psychopath. **13**:289 (April) 1933.

Two cases of progressive cerebral sclerosis in children aged 3 years, one a boy and the other a girl, are recorded. Each had a normal birth and uneventful development until 18 months and 2 years of age, respectively, when progress ceased and rapid physical and mental retrogression commenced. Each died soon after admission to the hospital. Postmortem examination revealed diffuse demyelinization of the white matter of the cerebral hemispheres and degeneration of the intrafascicular oligodendrocytes with a marked accumulation of masses of mucinoid and abnormal lipoid granules.

Jahr, Omaha.

Size in Mental Deficiency. W. R. Ashby and R. M. Stewart, J. Neurol. & Psychopath. **13**:303 (April) 1933.

This study was undertaken to ascertain how size varies among fully grown aments at different mental levels and to provide a background for further studies of particular parts, especially that of the nervous system. The authors assume that not only is there a handicap in the size of the mental defective's brain, but there is a general defect in size. Measurements of 269 defective persons showed that the size of the head diminished with decreasing intelligence, the defect being most marked in the idiot. A proportionate defect in size was observed in all determinations made: weight, length of the arm and the foot, length, breadth and height of the head, and distance from ear to ear. Mental deficiency may therefore be considered a general arrest in development rather than merely a cerebral anomaly.

Jahr, Omaha.

Diagnostic Significance of Babinski's Sign in Infants. Sieyro, Galicia clin. **5**:125 (March) 1933.

Babinski's sign is well known to indicate a lesion of the pyramidal tract involving its complete disintegration. This is not the case in infancy. In adults, a well marked typical dorsal flexion occurs. In infants, on the contrary, this is seldom distinct, there being many instances exhibiting a false Babinski sign. This appears to be a phenomenon indicative of a process involving a pyramidal lesion in the developmental period. Some doubt exists as to the age at which development of the direct motor tract is completed. Bendix places it at 6 months, Curschmann at 3 months and other authors, among whom are Laurent and Cornil, at between 9 and 12 months and even later in the case of delayed development. Sieyro investigated the reflex in a large number of children from 1 month to 2 years of age in the Santiago Hospital of Coruña. In the first three months a false Babinski sign was constant; it occurred during the second trimester in 60 per cent, during the third in 40 per cent, during the fourth in 25 per cent, during the fifth in 15 per cent, during the sixth in 9 per cent and during the seventh in 6 per cent. The author considers that this result sustains his belief that Babinski's sign is physiologic in the early months of life, and that no period can be set at which it begins to become pathologic. Nevertheless, it may be asserted that after three years dorsal flexion of the great toe denotes an interruption of the corticospinal motor tract.

Vinton, Brooklyn.

Treatment of Chorea with Phenyl-Ethyl-Hydantoin. Ihsan Hilmi, Monatschr. f. Kinderh. **58**:200, 1933.

Favorable results were achieved in five cases of chorea with the use of 0.4 Gm. daily of phenyl-ethyl-hydantoin. From six to ten days after starting treatment the usual reaction developed, with fever, an exanthem, eosinophilia and lymphopenia. This lasted from four to six days. Two weeks after the reaction, the cases showed marked improvement.

Gerstley, Chicago.

ANATOMIC TYPES OF GLIOMA OF THE BRAIN. P. SCHWARTZ, Nervenarzt **5**:449 (Sept. 15) 1932.

Schwartz expresses the opinion, based on an anatomic study of four hundred cases of intracranial tumor, that intracerebral neoplasms like meningiomas show a predilection for certain areas. He has been able to classify his material on gliomas into definite groups, the tumors in each group, though different histologically, being practically identical as to point of origin, mode of extension and general contour. The present contribution is limited to cases in which the growth had invaded the cortex. Tumors of the anterior superior callosohemispheric angle, which arise in the angle between the superior surface of the corpus callosum and the medial surface of the hemisphere, are divided into four subgroups, largely according to the cortical areas involved. The extension of all tumors in this group is limited inferiorly by the lateral prolongation of callosal fibers into the corona radiata. None of the foregoing (and of two other types of neoplasm of the frontal lobe, tumors of the inferior and middle frontal convolutions, respectively, only the latter) invade the frontal pole. A fourth type, which takes its origin below the knee of the corpus callosum, extends back into the gray matter of the hypothalamus and across the midline into the opposite hemisphere. Five types of tumor of the temporal lobe are presented, i. e., tumors of the superior, middle and inferior temporal gyri and tumors of the fusiform and hippocampal gyri.

With further experience Schwartz hopes to be able in every case to predict, from the area of the cortex involved, the location and the extent of the infiltrating process in the deeper structures. So far he has been successful in this respect. His experience to date also permits the hope that it may be possible to classify the various types of glioma clinically as well as anatomically.

DANIELS, Denver. [ARCH. NEUROL. & PSYCHIAT.]

HYPERTENSION AND ENCEPHALITIS. O. HERZ, Ztschr. f. Kinderh. **54**:273, 1933.

A case of hypertension following encephalitis in a boy, aged 5 years, is reported.

SHELLING, Baltimore.

## Diseases of the Eye

AN UNUSUAL CORNEAL LESION PROBABLY CONGENITAL AND FAMILIAL IN CHARACTER. G. E. DE SCHWEINITZ and A. COWAN, Am. J. Ophth. **16**:7 (Jan.) 1933.

A man, aged 48, exhibited numerous dotlike lesions in each cornea. These lesions were distributed over the entire cornea but much more densely in the center. The biomicroscope showed them to be in or immediately beneath Bowman's membrane. By direct illumination they appeared to be well defined, solid gray, plaquelike spots of various sizes and shapes, the largest measuring about 0.08 mm. across. The corneal epithelium was not involved and did not stain with fluorescein. The patient's son and daughter exhibited similar corneal disturbances. All had fairly high refractive errors, and the daughter had a convergent squint. The man's wife and another son did not have such lesions. The case of a man, aged 68, who presented a similar condition is also reported. The vision of all these persons was corrected to normal, except in the daughter with squint and in one eye of the father, in which vision of 6/7.5 was obtained. The authors consider the condition to be congenital and probably familial.

REESE, Philadelphia. [ARCH. OPHTH.]

LEPTOTRICHOSIS CONJUNCTIVAE (PARINAUD'S CONJUNCTIVITIS). F. H. VERHOEFF and M. J. KING, Arch. Ophth. **9**:701 (May) 1933.

The senior author has shown that there is a disease of the conjunctiva accompanied by massive inflammatory enlargement of the preauricular or other lymph glands. The conjunctival lesions appear as gray or yellowish areas beneath the

epithelium. Histologically, they are localized infiltrations of the tissues with macrophages loaded with broken-down chromatin. By a delicate method of staining the senior author has been able to demonstrate a leptothrix within the conjunctival lesions and reports three cases in which the diagnosis was made clinically and histologically.

WESCOTT, Chicago.

CONGENITAL READING DISABILITY—STREPHOSYMBOLIA. L. L. MAYER, J. A. M. A. **100**:1152 (April 15) 1933.

The author reviews the literature on strephosymbolia and reports three cases. In all the cases it was demonstrated that the center of auditory memory was entirely normal. This factor was used as an adjunct in teaching children with this condition. Travis' statement that handedness is the sine qua non of laterality would not seem to be borne out by these cases; neither is it evident that Gould's explanation that eyedness is determined by defects in one eye which cause the other to become dominant would apply in such cases. From a perusal of this small group of cases, weight is added to Orton's statement: "The master eye has been held by some to be a safer guide to native dominance than the master hand." The fact that early training may reverse the master hand while no amount of training has been able to change the master eye would seem to enhance the importance of determining eyedness. Histopathologic changes in the center for speech have not been studied in this type of case but may in the future reveal an anatomic foundation for the difficulty.

The author draws the following conclusions:

In five cases of acquired, congenital and partial word blindness (strephosymbolia), ocular dominance has been the outstanding feature.

It is important to determine the dominant eye; this knowledge is of value to the ophthalmologist and to the patient.

It is hoped that, by bringing such a condition to the attention of the ophthalmologist, a saner regard for children with partial word blindness will be stimulated and thus the stigma of being called "mental defectives" will be lifted from them.

ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

STRABISMUS—A PLEA. I. JENKINS MIKELL, J. South Carolina M. A. **29**:162 (July) 1933.

The author prefers charges against the pediatricians or those who practice pediatrics for not referring cases of squint to the ophthalmologist. He reviews twenty-five cases which have come under his direction, of which seven came to operation and nine gave good results with only corrected refraction. The youngest child of the series was 18 months old. The earlier the squint is corrected, the better the result.

ARSTON, JR., Columbia, S. C.

THE BLIND AND VISUALLY HANDICAPPED IN WEST VIRGINIA. J. E. BLAYDES, West Virginia M. J. **29**:293 (July) 1933.

While West Virginia has two schools for the blind, one for white people and one for the colored race, she is falling short of her duty to these handicapped persons. It is estimated that there are about 3,500 blind and visually handicapped persons in the state, of whom between 400 and 800 are of school age; yet the total average attendance of the two schools is only 137. The personnel of the two schools is of high standing, but facilities and follow-up work are lacking.

Examination of the 114 students at the school for white persons at Romney indicated that surgical intervention would benefit 27. The Lions Clubs of West Virginia financed the transportation and the hospitalization of these 27 at Bluefield, W. Va., where they were operated on by Blaydes. As a result, 9 returned to school with normal vision and 16 were benefited, acquiring vision varying from 20/50 to 20/200; 2 were not benefited.

Notwithstanding the splendid work done by the United States Public Health Service working in conjunction with the West Virginia State Board of Health, from October, 1915, to September, 1918, there is still much trachoma in the mountain sections. There must be more instruction in homes and institutions in regard to the prevention of avoidable injuries to the eyes. Employers and employees alike must be taught the importance of the use of goggles. There must be proper vocational education of the blind, and the federal government should provide institutions of higher education for the blind. There should be a state commission for the blind, and a state survey of the blind and visually handicapped is of the utmost urgency. Means of employment, at proper wages, should be provided for these persons, with aid in securing raw materials and in marketing their products, and campaigns of education to promote interest in the work of the blind and in the prevention and cure of blindness should be promoted.

SHAWKEY, Charleston, W. Va.

SOME EARLY OCULAR SYMPTOMS OF OVER-INDULGENCE IN SUGAR AND SWEET FARINACEOUS FOOD. A. MAITLAND RAMSAY, Brit. M. J. **1**:266 (Feb. 18) 1933.

The author is impressed with certain visual disturbances in children, particularly photophobia, which frequently accompany a diet high in carbohydrates. He describes the type of child in whom photophobia is observed, and has found that marked improvement follows the withdrawal of carbohydrate foods, especially sugar.

ROYSTER, University, Va.

DESIRABILITY OF ROENTGENOGRAMS OF THE CHEST IN CHILDREN SUFFERING FROM PHLYCTENULAR KERATOCONJUNCTIVITIS. R. PIERRET, A. BRETON and LOISON, Arch. de méd. d. enf. **36**:393 (July) 1933.

The relation of keratoconjunctivitis to scrofula has long been recognized. Believing that latent tuberculosis could be demonstrated in the great majority of cases, the authors conducted an intensive investigation in twenty-four cases. In 90 per cent there was a positive reaction of the skin, and in 30 per cent there were roentgenographic evidences of latent tuberculosis. The necessity for early separation of these children from the home environment, preferably in a preventorium, is apparent.

AMESSE, Denver.

## Diseases of the Skin

ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS WITH STAPHYLOCOCCAL PYEMIA IN A CHILD. E. SCHWARZ and F. PARKES WEBER, Brit. J. Dermat. **44**:486 (Oct.) 1932.

The authors report the case of a girl, aged 11 years, who had acute disseminated lupus erythematosus with fatal staphylococcic pyemia from some undiscovered source. No postmortem examination was permitted, but the authors think that in the absence of any signs of tuberculosis and with a negative Pirquet reaction it seems reasonable to suppose that the eruption was a cutaneous syndrome, and that it should be regarded as a manifestation of the staphylococcic infection, just as in various other cases the eruption has been regarded as a manifestation of streptococcic or of other infections.

WIEN, Chicago. [ARCH. DERMAT & SYPH.]

URTICARIA PAPULOSA: WITH NOTES OF FOURTEEN CASES WITH AN UNUSUAL HISTORY. J. KINNEAR, Brit. J. Dermat. **45**:65 (Feb.) 1933.

Clinical notes are given of fourteen children varying in age from 7 months to 9 years, in whom urticaria papulosa developed after they arrived in England from America. In two families more than one member was attacked at the same time.

In some cases the eruption was present when the patients landed; in others, its appearance was delayed for one month. No food factor was found to cause the condition. The actual exciting cause was not found. The inference is made that Hallam is correct in considering the condition as probably associated with the sleeping conditions at home.

WIEN, Chicago. [ARCH. DERMAT & SYPH.]

TUBERCULOUS INFECTION WITH ERYTHEMA NODOSUM. H. GORDON, Brit. J. Dermat. **45**:69 (Feb.) 1933.

A child, aged 3 years, presented a primary tuberculous lesion on the left side of the chin and a swollen submaxillary gland. An eruption was present on both legs below the knees; it appeared to be typical erythema nodosum, except that the nodes were barely tender. The eruption on the legs appeared about one week after the lesion on the chin. The submaxillary gland was excised. The Mantoux tests were negative in dilutions of from 1 : 1,000,000 to 1 : 1,000. When the patient was seen again four and one-half months later, the lesion on the chin was a definite lupus nodule, and there was a well healed scar over the previous site of the submaxillary gland. The Mantoux test was positive in a dilution of 1 : 1,000,000.

Gordon believes that unless one regards the appearance of erythema nodosum as a coincidence, this case appears to be an example of the condition occurring as a signal of a systemic invasion by the tubercle bacilli.

WIEN, Chicago. [ARCH. DERMAT. & SYPH.]

ERYTHROEDEMA. E. C. WARNER, Proc. Roy. Soc. Med. **26**:1005 (June) 1933.

Warner reports a case of erythredema in a child aged 19 months.

WILLIAMSON, New Orleans.

TREATMENT OF FURUNCULOSIS AND MULTIPLE ABSCESSES IN THE NURSLING BY IMMUNOHEMOTHERAPY. MAMERTO ACUNA and FELIPE DE FILIPPI, Arch. argent. de pediat. **3**:721 (Nov.) 1932.

The treatment consisted in preparing an autogenous vaccine from a furuncle or abscess of the affected infant. The vaccine was then injected into one of the parents; 1 or 2 cc. of the vaccine, which contained 100,000,000 bacteria, was injected every three days.

Twenty-four hours after the first injection, from 5 to 20 cc. of blood was withdrawn with a syringe containing 5 per cent solution of sodium citrate; the mixture was immediately injected into the buttock or under the skin of the abdomen of the infant.

The treatment was decidedly effective in the few cases reported.

SCHLUTZ, Chicago.

INCUBATION TIME OF ERYTHEMA NODOSUM. DÉNES VON MÓRITZ, Arch. f. Kinderh. **99**:177 (May 30) 1933.

Three children with no history of contact with tuberculosis were admitted to the hospital and were found to have a negative reaction to tuberculin. In the hospital they were exposed to patients with open tuberculosis. Within from five to six weeks later, typical erythema nodosum developed in each of the three children and the tuberculin test gave strongly positive results. These observations furnish further confirmation of the view that erythema nodosum is caused by tuberculosis and that erythema nodosum appears toward the end of the incubation period of tuberculosis when allergy to tuberculin arises.

LEMASTER, Evanston, Ill.

ICHTHYOSIFORM ERYTHRODERMIA (ERYTHRODERMIE CONGÉNITALE ICHTHYOSIFORME OF BROCQ, KERATOSIS RUBRA CONGENITA OF RILLE). WOLFGANG GASPER, Dermat. Wchnschr. **96**:150 (Feb. 4) 1933.

The patient was a 9 year old boy who had an extensive keratotic eruption that was most marked on the trunk and around the joints. It had developed gradually, starting when the patient was about 6 months of age. However, when the patient was even younger the skin had remained persistently redder than normal. The face, hands and feet were relatively free. No bullae had occurred. The hair and nails apparently grew more rapidly than is normal. There was no history of other cases in the family.

L. TAUSSIG, San Francisco. [ARCH. DERMAT. & SYPH.]

THE FUTURE OF CHILDREN WITH ERYTHEMA NODOSUM. D. OROSZ, Monatschr. f. Kinderh. **58**:180, 1933.

A follow-up study of sixty-four cases of erythema nodosum was made to determine whether the disease is primarily rheumatic or tuberculous. The authors conclude that there is absolutely nothing of a rheumatic nature in the disease, as in none of their cases did any rheumatic symptoms develop over periods up to eight years. There seems to be a tuberculous element in the disease, though in this respect the patients may be classified in two groups. In the first group, those with simple erythema nodosum which disappeared with the first attack, no further consequences were noted. In the second group of patients, in whom the erythema nodosum had a chronic course with frequent exacerbations, much active tuberculosis developed.

GERSTLEY, Chicago.

ECZEMA. G. A. ROST, München. med. Wchnschr. **80**:287 (Feb. 24) 1933.

In a lengthy article Rost shows that many cutaneous disorders which are called eczema are not true eczemas. Etiologically, the term eczema should not be used. He discusses mycotic, seborrheal and scrofulous eczema and eczema of the leg due to varicose veins.

BRAHDY, Mount Vernon, N. Y.

SKIN TURGOR OF SUCKLINGS. H. PAFFRATH and W. RIECKE, Ztschr. f. Kinderh. **54**:380, 1933.

This is the description of an apparatus for measuring skin turgor. The principle of the apparatus consists in measuring the retraction force (elasticity) of a fold of skin of certain size, the force being registered graphically.

SHELLING, Baltimore.

SKIN TURGOR IN NUTRITIONAL DISTURBANCES. W. RIECKE, Ztschr. f. Kinderh. **54**:385, 1933.

The skin turgor of fifty children with acute and chronic nutritional disturbances was found to be below normal. The lowest values were observed in cases of intestinal intoxications, but cases of dyspepsia without intoxication also showed low values. Weight and skin turgor are not always parallel; improvement in turgor usually precedes the hydration of the subcutaneous tissues.

SHELLING, Baltimore.

A FATAL CASE OF HEMANGIOMA CAVERNOSUM CONGENITUM. A. S. PETTERSSON and R. ROMANUS, Acta pædiat. **14**:417 (April 28) 1933.

At birth the infant showed a large cavernous hemangioma, which formed a tumor on the left shoulder. The tumor increased in size and developed spontaneous ecchymoses, causing the patient to be admitted to the hospital at the age of 2 months. Roentgenograms showed symmetrical invasion of the superior

mediastinum. Stridor, cough and cyanotic attacks appeared and increased in severity. The patient died at 5 months of age of bronchopneumonia. At autopsy, the tumor, histologically benign, was found to have invaded the thoracic cavity by extension, displacing the thymus upward and greatly compressing the primary bronchi.

McINTOSH, New York.

## Surgery and Orthopedics

INTRAVENOUS UROGRAPHY AFTER MAYDL'S OPERATION FOR EXSTROPHY OF THE URINARY BLADDER. R. SIMON and A. BRUNSCHWIG, Am. J. Roentgenol. **27**:103 (Jan.) 1932.

The authors report intravenous urography in a boy following Maydl's operation, skiodan being used. The advantages are that it is less toxic, and that the dose needed is smaller. The advantage of intravenous urography in these cases is the roentgen visualization of the ureterocolonic junction. With this the integrity of the transplanted ureters or the trigon can be easily controlled should there be any question of integrity during a postoperative complication. The dilatation of the ureters in the reported case cannot be explained. The reflux of the hepatic flexure indicates that not only the rectal and sigmoid portions but the entire colon serves as a reservoir for the urine.

STULIK, Chicago.

ROUTINE CIRCUMCISION IN INFANCY. W. R. SWARTZWELDER, Arch. Pediat. **50**:288 (April) 1933.

The author records his objection to routine circumcision in infancy and believes that a great many infants can and should be spared this common operation. The indications for circumcision are listed as follows: a narrowed, elongated prepuce, a very tight foreskin with a minute preputial opening and a densely adherent prepuce, and certain cases of paraphimosis. It is debatable whether routine circumcision should be advised (1) as a hygienic measure, (2) to prevent masturbation or (3) to render the person less susceptible to venereal infections. Without other definite indications for circumcision, Swartzwelder believes that this operation is unnecessary.

WADDELL, JR., University, Va.

ACUTE SURGICAL ABDOMINAL CONDITIONS IN CHILDREN. BERNARD PORTIS, Illinois M. J. **43**:222 (March) 1933.

In 158 patients operated on by Portis, acute appendicitis was the most frequent acute surgical lesion and was represented by 145 cases. In general, appendicitis in the first two years of life presents a bizarre picture which renders early diagnosis difficult. In children over 2 years of age the symptomatology is more like that of the adult form. The onset in most of the children was not sudden and was ushered in by colicky attacks of abdominal pain ranging from mild to severe. In the majority of cases the pain was generalized. Some form of gastro-intestinal disturbance was constant, although vomiting occurred in only 77 per cent of the patients, while others complained of anorexia and nausea. Fever was present in all the patients within the first twenty-four hours. Leukocytosis of from 12,000 to 20,000 was the rule. Physical findings were usually definite. However, some children with advanced appendicitis frequently presented the outward appearance of comparative comfort. Rebound pain, elicited by suddenly letting up the compressing hand, was found in the patients with peritoneal inflammation or free exudate. Involuntary muscular rigidity was sometimes difficult to ascertain but, when present, was diagnostic. Rectal examinations were always performed. Peritonitis other than of appendical origin was rare. Two cases of congenital atresia and six cases of intussusception were seen.

BARBOUR, Peoria, Ill.

ABDOMINAL EMERGENCIES IN INFANCY AND CHILDHOOD. EDWIN M. MILLER, Illinois M. J. **43**:569 (May) 1933.

The incidence, symptoms and surgical treatment of the abdominal emergencies with which the author has had experience are discussed. The clinical conditions discussed are amniotic hernia, congenital defect of the alimentary tract, congenital pyloric stenosis, intussusception, strangulated hernia, abnormalities of Meckel's diverticulum, acute appendicitis and acute mechanical intestinal obstruction.

BARBOUR, Peoria, Ill.

ETIOLOGICAL FACTORS OF ACUTE APPENDICITIS. ANFIN EGDAHL, Mil. Surgeon **73**:61 (Aug.) 1933.

In 1922 the rate of incidence of appendicitis increased sharply in the Puerto Rican forces, jumping from 1.66 per thousand persons for 1921 to 5.52 in 1922. This coincided with the epidemic of beriberi in this force due to polished rice. As soon as the deficiency of vitamin B was corrected, not only did the beriberi disappear but the rate for appendicitis fell to 1.26 in 1923. Evidence points to the fact that the increase in appendicitis coincided with the increased use of refined foods or of foods greatly altered in their composition by methods of preservation and preparation. Apparently vitamin B has a protective function in the gastrointestinal tract, as its absence or great diminution seems to favor the occurrence of appendicitis. It is possible that the other vitamins also have a protective function. In some cases recurring attacks of appendicitis may be prevented by proper food and by correcting unhygienic habits in the patient.

SANFORD, Chicago.

MECKEL'S DIVERTICULUM IN CHILDREN. HENRY W. HUDSON, JR., New England J. Med. **208**:525 (March 9) 1933.

The author reports forty-five cases, and includes thirty-two previously reported cases. There were thirty-five recoveries and ten deaths. In fourteen cases, four of which showed perforation, mucosa of the gastric type with ulceration and hemorrhage was found. In nine cases, there was intussusception; in six, diverticulitis; in seven, intestinal obstruction other than intussusception, and in one case each, umbilical fistula and duplex ileum.

Clinically, there was a history of either a chronic interrupted or an acute melena, accompanied by abdominal discomfort or paroxysmal colicky pain, nausea and sometimes vomiting. There were thirty male and fifteen female patients. The youngest patient was 4 hours old at the time of operation, and the oldest, 12 years. In only one case was a correct preoperative diagnosis made by roentgenograms. Confirmatory evidence of a secretion of the gastric type in the diverticula presenting mucosa similar to that of the stomach was found in one case. The method of excision and inversion by purse-string-suture is condemned.

GENGENBACH, Denver.

LOW PERICARDIOTOMY FOR ACUTE SUPPURATIVE PERICARDITIS. P. E. TRUESDALE, New England J. Med. **208**:671 (March 30) 1933.

The author discusses in detail the entire series of 152 operative cases of acute suppurative pericarditis reported to date in the literature. His summary follows:

1. Acute suppurative pericarditis commonly is a secondary infection attacking a patient when his vital capacity has been reduced by the primary infection.

2. It is insidious, concealed, progressive and, without intervention, almost invariably fatal.

3. The infection is seldom recognized clinically. Diagnosis is not difficult if the examiner knows what to look for.

4. The mortality among those treated by operation varies from 38 to 65 per cent.

5. Next to early diagnosis and immediate intervention, adequate drainage is the essential factor in recovery.

6. The extreme lateral and most dependent area of the pericardium is the point of election for drainage.

7. Incision of the pericardium at its most dependent point should not be less than 6 cm. long, through a correspondingly large incision in the wall of the chest.

GENGENBACH, Denver.

HERNIA IN THE INFANT, WITH A REPORT OF THIRTY-ONE CASES. W. J. BLEVINS, Surg., Gynec. & Obst. **55**:505 (Oct.) 1932.

In 906 consecutive cases of hernia observed in the Woodland Clinic Hospital, California, 20 were found in children under the age of 42 months. Three of the patients were cretins, with wide diastasis recti. Twenty-six patients underwent radical herniorrhaphy, without mortality or a recurrence. Eleven other cases were observed within the same age range. The author makes the following recommendations:

1. All inguinal and femoral hernias persisting over a period of one month should be referred to a surgeon for hernioplasty. Incarceration calls for immediate surgical intervention to insure against strangulation.

2. A truss is not to be used, as its damage outweighs the occasional advantages.

3. True congenital umbilical hernia should be referred for operation a few days after birth. Enlarged umbilical ring should be treated conservatively with a gauze pad and adhesive strapping. If the ring is still open after six months, the condition should be referred for operation.

4. The large hernia of the cretin due to complete separation of the rectus muscles is not a surgical condition and calls for the administration of thyroid extract.

GRAVES, New York.

ESOPHAGEAL PERFORATION IN EMPYEMA. M. MIKULA, Časop. lék. česk. **70**:1818 (Dec. 18) 1931.

A girl, aged 11, with frank empyema, had bronchitis and erysipelas at 1 year of age, and chickenpox and pneumonia at 8 years. She also had severe pneumonia of recent date. Following resection of a rib, milk which was taken by mouth came through the incision immediately. Following gastrostomy, the sinus gradually healed. The roentgenograms of the various stages are presented. A review of the literature is included.

STULIK, Chicago.

## Miscellaneous

SODIUM DEHYDROCHOLATE IN ARSPHENAMINE POISONING: A PRELIMINARY REPORT. BERNARD APPEL, Arch. Dermat. & Syph. **27**:401 (March) 1933.

In this article the author describes the use of sodium dehydrocholate (given intravenously at intervals of several days in doses of 10 cc. of a 5 per cent solution) to combat the reactions resulting from arsphenamine and its derivatives in the treatment of syphilis. He believes that this drug is valuable and prompt in combating jaundice, nausea and vomiting (the three most frequent gastro-intestinal reactions to arsenic). He includes a review of the literature concerning the history, properties, action and use of this drug.

EKERMEYER, Iowa City.

PULMONARY EMBOLISM FROM ARSENICALS INJECTED INTRAVENOUSLY: A METHOD SUGGESTED FOR PREVENTION. GEORGE C. SHIVERS, Arch. Dermat. & Syph. **27**:901 (June) 1933.

About 800 deaths are caused annually in the United States by arsenical drugs. A large number of these are due to pulmonary embolism. This accident is believed to occur when the drug is given in an acid solution ($p_H$ below 7), causing com-

bination of the drug with the plasma proteins. The author describes and suggests a usable and accurate method of preventing this complication. This includes the addition of the indicator bromthymol blue to the drug in the ampule, enabling the physician to determine the correct reaction of the solution for safe administration. The author also reviews the reports of 18 cases in which death occurred from pulmonary emboli in persons treated with arsenicals (and the report of one case in which death occurred with mersalyl). EKERMEYER, Iowa City.

HEALTH CONDITIONS IN NEW YORK STATE, NOVEMBER, 1932. Health News (New York) **10**:10 (Jan. 16) 1933.

The birth rate in New York State for November, 1932 (14.2 per thousand persons), was practically the same as in the corresponding month of 1931, in which it was the lowest on record. The general death rate (10.6 per thousand) and the infant mortality rate (52 deaths under 1 year per thousand infants alive at birth) have never been lower. When the complete returns for the year are analyzed, they will undoubtedly show the lowest birth, death and infant mortality rates ever known in the state. A new low mortality rate for diphtheria (0.9 per hundred thousand) was established in November, 1932. AIKMAN, Rochester, N. Y.

A NEW TYPE OF MONOXIDE ACCIDENT. Health News (New York) **10**:12 (Jan. 16) 1933.

A boy, aged 9 years, attached his sled to the rear of an automobile near the exhaust pipe. He is said to have become unconscious from carbon monoxide poisoning, although he was in the open air. AIKMAN, Rochester, N. Y.

NEW LOW FOR MILKBORNE EPIDEMICS. Health News (New York) **10**:26 (Feb. 13) 1933.

The year 1932 gave a new low record for milk-borne outbreaks of communicable diseases in New York State exclusive of New York City. Two small outbreaks, both of typhoid fever occurred, with a total of 16 cases. In 1927, 20 cases were reported; in 1930, the total was 633. There have been 103 outbreaks within sixteen years, with a total of 3,759 cases. Of these outbreaks, 101 were traced to raw milk. New York City, which requires all milk other than certified to be pasteurized, had but 1 outbreak in these years. Ninety per cent of the outbreaks have originated at dairy farms. AIKMAN, Rochester, N. Y.

X-RAY TREATMENT OF SOME INFLAMMATORY CONDITIONS IN CHILDHOOD. SAMUEL J. LEVIN, J. Pediat. **2**:312 (March) 1933.

Excellent clinical results were obtained by the use of roentgen therapy in inflammatory conditions such as acute lymphadenitis and acute mastoiditis. In some cases of chronic otitis media and mumps favorable reactions followed roentgen irradiation. The author believes that roentgen therapy of inflammatory conditions in childhood is deserving of greater and more widespread trial. LEMASTER, Evanston, Ill.

A STUDY OF CHILD CARE IN THE FIRST TWO YEARS OF LIFE. RUTH W. WASHBURN and MARIAN C. PUTNAM, J. Pediat. **2**:517 (May) 1933.

Fifty-nine infants at a well baby conference were studied to determine how the mothers were managing their babies, what problems arose and how a psychologist might be of aid. The authors suggest that individual differences in infants are too little stressed in the literature; the result is undue anxiety on the mother's part when her infant is found to deviate from the accepted standards. Of the forty-six infants studied more than once, twenty-seven presented practically no problems; thirteen presented a succession of transient minor problems, and six

evidenced persistent difficulties. Further education of the community with respect to the type of question a psychologist is equipped to answer is necessary before he can be of maximum usefulness. LEMASTER, Evanston, Ill.

PROGRESS OF PUBLIC HEALTH AS IT RELATES TO THE CHILD. HAROLD C. STUART, J. Pediat. **2**:756 (June) 1933.

In this critical review, the present status of public health work in the United States is considered. Progressive movements in this field during recent years are cited, and the needs of the future are pointed out. The rôle of the public health officer has changed from that of an inspector or a police officer to that of an educator. The purpose and function of federal, state, local and nonofficial health organizations are described, with special reference to the services for infants and children. More money is spent by most American communities for sanitation and less for laboratories, nursing services and maternal and child hygiene than conditions justify. Public health services are nowhere able to perform fully the work which present knowledge would indicate. LEMASTER, Evanston, Ill.

PEDIATRICS: WHAT IS IT? WILBUR C. DAVISON, J. Pediat. **3**:64 (July) 1933.

After analyzing the incidence and mortality of all diseases of infants and children, Davison finds that the most important diseases are those which can be prevented or cured. The pediatrician should concentrate on the conditions amenable to treatment and teach the medical student to become familiar with them. Pediatrics can be of the greatest service to the public if, in its practice, emphasis is placed on the prevention of disease and on periodic examinations of children for the early detection of disease, rather than on consultative service. Investigators of the White House Conference found that the health of children who were brought regularly to a physician's office was better than that of those who had medical care only during acute illnesses. LEMASTER, Evanston, Ill.

OPTICALLY ACTIVE HYDANTOINS AS HYPNOTICS. HARRY SOBOTKA, S. M. PECK and JOSEPH KAHN, J. Pharmacol. & Exper. Therap. **47**:209 (Feb.) 1933.

Phenyl-ethyl-hydantoin (nirvanol) may be toxic to human beings, causing a rash, fever and other symptoms, the reaction commonly called nirvanol disease. In an attempt to do away with the toxic effect and leave the useful therapeutic effect, dextrorotatory and levorotatory forms were obtained from the racemic drug. The levorotatory form caused nirvanol disease in 64 per cent of fourteen children, with about one-half the total effective dose of racemic nirvanol; the latter, however, caused toxic symptoms in 84 per cent of twenty-five children. The dextrorotatory form caused nirvanol disease in but 28 per cent of eighteen children, with about one-half the total racemic dose, while the sedative action was similar.

The abstractor is unable to agree with the conclusion that the curative effect is independent of the nirvanol disease produced by the drug.

Results in chorea are to be reported elsewhere. PILCHER, Cleveland.

IMPORTANCE OF POSTURE IN HEALTH. B. M. COUTER, M. J. & Rec. **137**:483 (June 21) 1933.

Correct body mechanics is of definite importance in maintaining good health. Poor posture predisposes to and causes chronic strain. The commonest complaints are foot strain, backache, fatigue, neuritis and pain in the joints. Neglect of good body mechanics results in bad effects on the vital functions.

WILLIAMSON, New Orleans.

# Society Transactions

## NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

*Regular Meeting, Jan. 11, 1934*

MARTHA WOLLSTEIN, M.D., *Presiding*

ENLARGED COLORED TRANSPARENT SECTIONS OF THE LUNG, SHOWING VARIOUS FORMS OF PNEUMONIA. DR. CHARLES HENDEE SMITH, DR. IRVING GRAEF and DR. ELIZABETH T. ANDREWS.

(These were demonstrated by lantern slides.)

ANAPHYLACTOGENIC PROPERTIES OF THE PURIFIED MILK PROTEINS AND OF RAW, EVAPORATED, SUPERHEATED, DRIED AND ACIDIFIED MILK. DR. BRET RATNER and H. L. GRUEHL.

This article will appear in full in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

HEMATOGENOUS DISSEMINATION IN TUBERCULOSIS OF CHILDHOOD. DR. EDITH M. LINCOLN.

Knowledge of the pathogenesis of tuberculosis in children has been revolutionized within the past fifteen years. Physicians now conceive of tuberculosis as a systemic disease and believe that some bacilli enter the blood stream in all cases of primary tuberculosis. Bacteriologic proof exists that tubercle bacilli circulate at times in the blood of tuberculous persons, but the technic for demonstrating them is far from perfect, so that the percentage of cases in which they may be found is uncertain.

Bacilli reach the blood from the nodes regional to the primary focus by way of the lymphatic duct, but massive infection producing acute generalized miliary tuberculosis is more generally due to erosion of the wall of a blood vessel by a caseating focus of tuberculosis or to the breaking down of an intimal tubercle.

The clinical picture is dependent on the number of tubercle bacilli conveyed to the blood stream, the frequency of repetition of this dissemination, the uncertain factors of allergy and the relative immunity of the body to the bacilli.

Four types of tuberculosis due to hematogenous dissemination can be distinguished clinically: (1) protracted generalization, which, when marked, is a clinical entity, showing a characteristic roentgenogram of the lungs and associated with panadenitis and panserositis; (2) the easily recognized acute generalized miliary tuberculosis; (3) a condition in which the predominant lesion—for instance, tuberculosis of a kidney or a bone—is the result of a hematogenous dissemination, though one is not accustomed to think of it in these terms; (4) occult tuberculosis, in which physical examination may either give negative results or show an enlarged spleen, palpable superficial nodes and cutaneous lesions, or in which the disease may be evident on roentgen examination of the lungs or, more rarely, of the spleen and cervical nodes. Calcified apical lesions due to hematogenous dissemination belong in this group, and a number of cases of these are being followed in the hope that they will throw new light on the development of tuberculosis in adults.

DISCUSSION

DR. W. GRETHMANN: During recent years I have been interested in hematogenous dissemination of tubercle bacilli in children and have been fortunate to observe in Dr. C. H. Smith's service of the Children's Medical Division at Bellevue

Hospital a group of cases which are of unusual interest because of the dissemination of tuberculosis after the primary infection. In the interpretation of these cases, which were analyzed together with Dr. Lincoln and partially presented here, I wish to confine my remarks to the pathologic features. Until recently, it was not considered, as a rule, that hematogenous dissemination takes place after the primary infection. However, the evidence that such dissemination does take place in practically all cases of primary tuberculous infection is rapidly accumulating in our material. In support of this, I wish to refer to the case of a child 8 weeks of age. This case was also shown by Dr. Lincoln in her presentation. At autopsy, we found a caseous focus about three-fourths inch (2 cm.) in diameter in the upper part of the lower lobe of the left lung. This was interpreted as the primary focus of a tuberculous infection and it already showed a cavity about 0.5 cm. in diameter. Its regional bronchopulmonary lymph node was also considerably enlarged and caseous. Besides this evidence of primary tuberculous infection in the lungs, there were signs of hematogenous dissemination into the lungs and the spleen; tubercles the same size as miliary tubercles and smaller, and even larger tubercles, were found in both these organs. They were located predominantly in the apexes of both lungs. This case observed in a child of 8 weeks seems to me to be clearcut evidence that hematogenous dissemination takes place at the time of the establishment of the primary tuberculous infection. If it can be shown that such hematogenous foci, which in older children are referred to as Simon foci, originate from the first tuberculous infection, and if it can be shown that these foci break down later on into chronic pulmonary tuberculosis, these facts may influence physicians to alter considerably their conception of the pathogenesis of chronic pulmonary tuberculosis. Up to now it has generally been believed that chronic pulmonary tuberculosis is the effect of another exogenous aerogenous reinfection. In my opinion, evidence is rapidly accumulating to show that in the origin of chronic pulmonary tuberculosis not only exogenous aerogenous reinfection has to be considered but also hematogenous dissemination from an already existing tuberculous focus within the body, if not from the focus of the primary tuberculous infection itself.

DR. J. B. AMBERSON: Through an arrangement for cooperation between the tuberculosis service and Dr. Smith's pediatric service at Bellevue Hospital I have had the privilege of following Dr. Lincoln's work, which has impressed me a great deal. Following Dr. Grethmann's pathologic demonstrations and Dr. Lincoln's clinical correlations, I have been able to identify the same types of hematogenous tuberculosis in adults, although of course they are less frequent after childhood. These types are particularly liable to occur in Negro adults, and the tendency to hematogenous dissemination in the acute and in the protracted form seems to be characteristic of this race. Only a few cases of the protracted type have been found in white adults. The work of Dr. Grethmann and some other pathologists lends weight to the conception that pulmonary tuberculosis in adults represents, at least in certain cases, an exacerbation of foci that were established in the apexes of the lungs shortly after the first infection in childhood. While the possibility of exogenous reinfection of adults must be given consideration, one cannot ignore the other possibility.

DR. CHARLES HENDEE SMITH: This is interesting from the clinical standpoint. Twenty years ago, when a pulmonary condition showed diffuse mottling roentgenographically it was called miliary tuberculosis. A little later such a condition was always called disseminated tuberculosis. Now it is known that a differentiation must be made between these conditions, both of which give a general mottling, but which have quite different prognoses. In childhood a bronchiogenic spread of tuberculous infection is a most serious matter, while lesions due to hematogenous dissemination are relatively benign, and patients with this condition get well at times. In Vienna I saw four practically well children who had had generalized hematogenous tuberculosis. Doctor Gardner of Saranac showed slides of the lungs

of a longshoreman killed in a brawl who had completely healed miliary tuberculosis throughout his lungs and was well enough to get drunk and get killed.

DR. BÉLA SCHICK: Lately physicians have been inclined to pay more attention to exogenous superinfection as the cause of tuberculosis in adults than before, when they traced all cases of tuberculosis in adults to extension of an endogenous infection of early childhood. Most likely both should be considered.

So far as the spread of miliary tuberculosis is concerned, one must remember that the lymphatic system connects with the blood stream, so that a part of the bacilli being spread in the lymph enter the blood. They go through the thoracic duct into the vena cava superior and from there into the right side of the heart and are carried through the pulmonary artery into the circulation of the lungs. After filtering through the capillaries of the lungs, they may go into the left side of the heart and reach the systemic circulation, and the possibility then exists of the production of tuberculous foci in different parts of the body, including the lungs. The same dissemination may occur if a tuberculous lymph node adjacent to the venous angle erodes the venous wall and directly invades the vena cava superior.

Hematogenous dissemination occurs in another way when a tuberculous lymph node erodes the wall of a branch of the vena pulmonalis. Tubercle bacilli, invading the venous circulation, reach the left side of the heart without previous filtration in the capillaries involved in the pulmonary circulation. In intensive invasion the great mass of tubercle bacilli reach all the organs directly and may produce tuberculous foci in the skin, joints, bones, etc. An intensive eruption of tuberculids in the skin suggests such an invasion.

Tuberculous meningitis may develop from a formerly established tubercle in the brain or as a part of the spread of miliary tuberculosis.

Recently the more frequent occurrence of miliary tuberculosis of the lungs during the early stage of a tuberculous disease has been pointed out. Miliary tuberculosis of the lungs may clear up in the early stage. The frequency of the circulation of tubercle bacilli in the blood stream (according to Löwenstein) needs to be studied extensively.

PARACENTESIS OF THE PERICARDIUM AS A THERAPEUTIC PROCEDURE. DR. LUCY PORTER SUTTON.

This paper will be published in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

SERUM TREATMENT OF LOBAR PNEUMONIA IN CHILDHOOD. DR. ROSA LEE NEMIR.

Antipneumococcic serum has been used extensively in the treatment of pneumonia in adults. For infections with some types of pneumococcus the mortality rate has been lowered following the administration of serum. At Bellevue Hospital we have been evaluating serum therapy for infections with similar types and for infections with the more recently isolated types so frequently found in infants and children.

Lobar pneumonia in children over 2 years of age is notably a benign disease; in those under 2 years it approaches in severity the pneumonia of adults. Bronchopneumonia is distinctly a very serious disease both in its course and in its mortality rate. Because of the low death rate for lobar pneumonia in children, criteria other than the effect on the mortality rate must be employed, namely, the effect on the duration of the disease and the effect on the complications.

This study was begun in January, 1932, and included clinical and bacteriologic observation of patients with all types of pneumonia. Dr. William H. Park and Dr. Charles Hendee Smith gave valuable suggestions as to the conduct of the investigation. The report is based on the study of 165 patients with lobar pneumonia associated with the types of pneumococcus for which therapeutic serums are available; 69 of the patients were treated, and the remaining 96 served as controls.

*Method.*—Following a cough productive of mucus the pharynx was swabbed and cultures were made in plasma broth. This material was injected into a mouse, and the original swab was used in streaking blood agar plates. The Sabin method for rapid typing was employed. Direct typing by the modified Neufeld method is now being used. Blood agar plates are extremely important in studying pneumonia in children. Staphylococci and streptococci are often significant etiologic factors.

A small percentage of error in bacteriologic diagnosis was found by this method. On several occasions the pneumococci obtained from the pharyngeal swab were probably normal inhabitants of the throat and not pathogenic for the patient. Occasionally a pneumococcus (usually type VI, a frequent inhabitant of the throat in children) was isolated from a swab and no other culture of that type ever obtained on repeated swabbing of the throat of the same patient.

The serums used were furnished by Miss Georgia Cooper from the Department of Laboratories and the Bureau of Research, New York City, and the financing was done largely by the Commonwealth but also by the Littauer and Altman Foundations.

No patient with a positive intracutaneous or ophthalmic reaction to a 1:10 dilution of serum was treated. The dosage for twenty-four hours was approximately from 300 to 800 units per pound of body weight, varying with the severity of the disease. Usually the first dose of serum was 2 cc. (irrespective of the potency) for a patient under 2 years of age and 5 cc. for one over 2 years, given intravenously. Intramuscular administration is not so effective in shortening the disease. No larger initial doses were given because of possible sensitivity to serum. The average dosage for twenty-four hours was from 6 to 9 cc. for patients under 2 years of age and from 10 to 25 cc. for those over 2 years. The potency of the serums varied from 400 to 1,500 units per cubic centimeter. One dose was usually given after the temperature had remained below 100 F. for from two to four hours. Frequently from three to four doses were sufficient, and never more than seven were given.

*Results.*—Pneumococcus type I was found to be the predominant infecting organism in lobar pneumonia in children over 2 years of age; it was present in 32 per cent of all children with pneumonia and in 47 per cent of those in which the condition was treatable. In patients under 2 years of age the predominant pneumococcus was found to be type XIV, which was present in 27 per cent of all infants with pneumonia and in 34 per cent of those in which the condition was treatable.

No appreciable difference was found between the mortality rates for lobar pneumonia in the treated and untreated patients. The deaths were few—2 in the treated and 3 in the untreated patients. In a small series of patients with bronchopneumonia there was a much lower mortality rate for the treated patients.

Serum definitely shortened the duration of the disease. A study of all patients receiving serum in comparison with a similar control group revealed a much earlier crisis, which occurred by the fifth day of the disease in 60 per cent of the patients treated with serum, as compared with 20 per cent for the control group.

The most satisfactory results were observed with serums prepared against pneumococcus types I and XIV. Striking results were obtained with type I serum. A crisis occurred as early as the third day in 5 of the 20 patients treated; no control patient had such an early crisis.

A study of the duration of type I lobar pneumonia with reference to the period of hospitalization revealed that early hospitalization does not in itself act to shorten the disease. Thirteen patients who received serum were admitted to the hospital on the second day of the disease. All had a crisis by the end of the fifth day, and most of them before. Nine patients who likewise were admitted on the second day of the disease and had equal hospital care, but who received no serum, had no crisis until from the sixth to the ninth day, the disease running a long course.

Of 18 patients treated with type XIV serum, 80 per cent presented a crisis before the seventh day, as compared with 19 per cent of the 27 patients in the control group.

Finally, only 1 of the 69 patients treated with serum subsequently showed empyema. Of the 96 patients in the control group, 7 later had empyema; in 4 of these the infecting organism was Pneumococcus type I, and in 3, Pneumococcus type XIV, VII and V, respectively. A spread of pneumonia to a new lobe was observed in 2 patients in the control group. No patient receiving serum later showed meningitis. Pneumococcic meningitis type XIV occurred in 1 patient in the control group. Three infants had pneumococcic meningitis type VI; all died; 1 of these had received intravenous and intrathecal injections of antipneumococcic serum.

It is difficult to devise an accurate quantitative method for evaluating a therapeutic agent. Observation of individual cases, however, has given us a definite impression that serum is of value in the treatment of pneumonia in children.

DISCUSSION

DR. JESSE M. BULLOWA: Permit me to congratulate the section on the excellent presentation by Dr. Nemir, who conclusively demonstrates that serum shortens the course of pneumonia. There is no statistical proof of the value of antipneumococcic serum in respect to life-saving ability; it will take a number of years and many workers to accumulate sufficient data for this, because of the numerous types of pneumococcus. One observer cannot encounter a sufficiently large series of cases in a single year to determine statistically the value of serum, if reduction of fatality is the criterion.

During the past five years we have been doing similar work at Harlem Hospital, with the cooperation of Dr. Morris Gleich, the pediatrician in charge. During this time we observed 445 cases of proved pneumococcic pneumonia in children. There were numerous types, and type XIV predominated. If one groups together the cases in which bacteremia occurs (a serious life-menacing condition), one may determine the effect of serum on it.

Two hundred and twenty-four of the children observed were under 2 years of age. As is shown in the table, 192 of this group did not receive serum; 38 of these

*Comparison of Mortality Statistics for Children with Pneumococcic Pneumonia in the Period from 1928 to 1933, According to Whether They Had or Had Not Received Specific Serum*

| | | Children Under 2 Years of Age | | | | | | Children 2 Years of Age and Over | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No Serum | | | Serum | | | No Serum | | | Serum | | |
| Pneumococcus Types | Total Number of Cases | Cases | Deaths | Per Cent | Cases | Deaths | Per Cent | Cases | Deaths | Per Cent | Cases | Deaths | Per Cent |
| I to XXXII | 445 | 192 | 38 | 19.8 | 32 | 8 | 25.0 | 179 | 8 | 4.5 | 42 | 2 | 4.8 |
| | | 9† | 7† | 77.7† | 7† | 3† | 42.8† | 7† | 3† | 42.8† | 4† | 0 | |

* This study was financed by the Littauer Pneumonia Research Fund of New York University.

† Cases in which the blood culture was positive.

died—a mortality of 19.8 per cent. Thirty-two received serum; 8 of these died—a mortality of 25 per cent. In 9 of the 192 patients who did not receive serum the blood was invaded; 7 of these died—a mortality of 77.7 per cent. In 7 of the 32 patients who received serum the blood was invaded; 3 of these died—a mortality of 42.8 per cent.

Two hundred and twenty-one of the children observed were over 2 years of age. One hundred and seventy-nine of these received no serum; 8 of these died—a mortality of 4.5 per cent—while of the 42 patients who received serum 2 died—a mortality of 4.8 per cent. In 7 of the 179 patients who did not receive serum the blood was invaded, and 3 of these died—a mortality of 42.8 per cent. In 4 of the 42 who received serum the blood was invaded, but none of these patients died.

DR. CAMILLE KERESZTURI: In Fifth Avenue Hospital we have been studying the effect of serum treatment on children for the past three years. As our service is smaller than that in Bellevue Hospital, we have been unable to collect as many cases as Dr. Nemir. Therefore, our present conclusions on the subject are based on clinical impressions rather than on statistical facts.

On the whole, we agree with Dr. Nemir that treatment with the specific pneumococcic serum shortens the course of the disease. Our method of coming to this conclusion was somewhat different from Dr. Nemir's. We averaged the durations of the disease in treated and nontreated patients and found that the average duration of pneumonia was ten days in those who received no serum and eight and a half days in those who received serum. We are confident that these figures are reliable, as we did not select patients for treatment because they had early pneumonia. We tried to select equal numbers of patients in whom the disease was caused by the same pneumococci for treatment and for control.

The mortality for our total group was 8 per cent irrespective of treatment, age of patients or clinical type of pneumonia. The mortality for lobar pneumonia in patients over 2 years of age was only 3 per cent both for those treated with serum and for the control group. This figure checks remarkably with the death rate for Dr. Nemir's group.

I wish to say a word about the significance of positive blood cultures in pneumonia. We cultured the blood one or more times in 65 cases. Positive cultures were obtained in 4. Two of the 4 patients died, which means an approximate mortality of 50 per cent. This figure is in marked contrast to the mortality already mentioned of 8 per cent for the total group, which included 1 patient with a positive blood culture. This patient survived. All the other patients of this group for whom cultures of the blood were made had negative cultures. We do not think that we can explain the high mortality in the group having the 4 positive blood cultures on the basis of age, as 2 of the 4 patients were less than 2 years of age, and 2 were more than 2 years of age. Of the 6 patients who died giving the 8 per cent mortality for the total group with negative blood cultures, 4 were less than 2 years, and 2 were more than 2 years of age. From this analysis, one is aware that a positive blood culture in a case of pneumonia means a severe prognosis. Therefore, even if one is not sure of the general usefulness of pneumococcic serum treatment for children, one should be extremely liberal in trying it in cases in which the blood culture is positive. We ourselves are not yet ready to recommend it as a routine treatment for cases in which the blood culture is negative.

We realize that if we type the cases according to the cultures from the throat swabs we may not be sure that we are giving the proper specific serums to the patients. There is always a possibility that the pneumococcus found in the throat is different from that which caused the disease. However, as Dr. Nemir mentioned, this discrepancy occurs in only 15 per cent of the cases. We tried to verify the findings from the throat swabs by cultivating material obtained from the lung by suction. We tried this in the cases of 28 patients; 24 of them had lobar pneumonia and therefore it was relatively easy to decide where to make the puncture. We found that the procedure was simple and that it was not followed by any complications. However, we gave it up, because we obtained positive results in cultures of material obtained by suction in only 17 per cent of the cases whereas in cultures of material from the throat swabs we found the specific

pneumococcus in 60 per cent of the cases on first examination. We do not find that we can decrease the time of typing by using lung suction.

We thoroughly agree with Dr. Nemir that a great deal more careful work is needed in several hospitals before physicians will be in a position to pass an opinion about the value of treating pneumonia in children with specific pneumococcic serums.

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## NORTH PACIFIC PEDIATRIC SOCIETY

*Midwinter Meeting, Seattle, Jan. 20, 1934*

ARTHUR H. GRAY, M.D., *in the Chair*

MENINGITIS TREATED WITH IRRADIATED BLOOD. DR. C. LUVERNE SMITH, Seattle.

A girl, aged 9½ years, complained of otalgia. Five days later, a swelling was noticed back of the left ear. Four days after this mastoidectomy was performed, and pus under pressure was found. The dura was exposed, revealing an exudate. Headache persisted following the operation, and six weeks later the child returned to the hospital with a temperature of 103.4 F. Three days later coma and paralysis occurred. The spinal fluid was clear and contained 720 cells and 90 mg. of sugar per hundred cubic centimeters, but no organisms. A swab from the mastoid yielded a pure culture of streptococci. Convulsions were almost continuous. Forced spinal fluid drainage was instituted. Irradiated blood was given on alternate days.

DISCUSSION

DR. V. K. HANCOCK, Seattle: The technic of using irradiated blood is to take the patient's own blood and irradiate it in a special chamber. There seems to be a secondary irradiation which is responsible for the destruction of both staphylococci and streptococci in the blood stream. There is usually a sharp increase of from 10 to 25 per cent in hemoglobin within three days.

DR. A. H. SPOHN, Vancouver, B. C.: How long does the increase in hemoglobin remain?

DR. V. K. HANCOCK, Seattle: The length of time has not been determined.

DR. C. U. MOORE, Portland, Ore.: Does the irradiated blood affect streptococci and staphylococci alike? What is the effect on tuberculosis?

DR. V. K. HANCOCK, Seattle: This method is probably more effective against streptococci. No work has been down on tuberculosis.

ACUTE RHEUMATIC FEVER WITH NO CARDIAC INVOLVEMENT. DR. FRANK H. DOUGLASS, Seattle.

A boy, aged 12 years, was presented, who over a period of fourteen weeks had shown all the symptoms and physical findings of acute rheumatic fever, with no involvement of the heart. No type of treatment seemed to influence the temperature although salicylates relieved the pain.

DISCUSSION

DR. A. H. SPOHN, Vancouver, B. C.: There seems to be no connection between the severity of the infection and cardiac complications. Salicylates in sufficient doses always relieve the pain.

DR. N. L. THOMPSON, Everett, Wash.: What is the significance of bradycardia in rheumatic fever?

Dr. F. R. Fischer, Spokane, Wash.: A supposedly specific strain of Streptococcus rheumaticus has proved to be of value in some cases in my practice.

Dr. E. J. Barnett, Seattle: The heart is probably damaged, even though no murmur is present.

Dr. Frank H. Douglass, Seattle: In this particular case, adenopathy and a large spleen may have acted as a focus to prolong the fever. Bradycardia probably means damage to the conduction system.

Treatment of Lobar Pneumonia. Dr. C. Luverne Smith, Seattle.

Eight cases of lobar pneumonia in patients in an institution were presented. In all these the onset had occurred on almost the same day. In each instance the diagnosis was confirmed by the recovery of pneumococci from the sputum and by roentgenograms. Four patients were treated by diathermy, and four by the ordinary methods, including the administration of oxygen. No benefits could be observed from the use of diathermy. Oxygen seemed to give relief in selected cases.

DISCUSSION

Dr. H. H. Skinner, Yakima, Wash.: Why did you use diathermy? What is the present opinion of the pneumonia jacket? Why are physicians again using oxygen? A few years ago it was deemed irritating to the air passages, but its use has recently been revived. I have been using epinephrine in pneumonia, apparently with some success.

Dr. H. T. Clay, Tacoma, Wash.: The mortality in this part of the country is low, regardless of the treatment.

Dr. N. W. Clein, Seattle: What about the old-fashioned mustard plaster?

Dr. A. H. Spohn, Vancouver, B. C.: The old-fashioned mustard plaster has been proved to have a beneficial effect on the trophic nerves.

Dr. A. E. Wade, Seattle: The mustard plaster gives a sense of well-being; I have learned that from personal experience. Then, necessarily, a pneumonia jacket should be used for protection.

Dr. A. Rembe, Seattle: What was the epidemic background in this infection?

Dr. C. Luverne Smith, Seattle: These various treatments are difficult to evaluate. Diathermy was tried because it seems to be of some value in adults. Oxygen made the respirations easier. The epidemic in the institution started as ordinary rhinitis.

Constipation. Dr. H. T. Clay, Tacoma, Wash.

It should be made clear to the mother that no real harm comes from failure of the child to have a bowel movement daily. In breast-fed infants, one must differentiate between a hard stool, or constipation, and a soft stool which the baby simply fails to pass. An infant may be taught by the age of 3 months to have a stool at a regular time, the mother supporting the child in an upright position. Glycerin suppositories have never been found harmful. A child may become a toilet sitter originally because of a hard stool, but the practice finally becomes a habit. Cure is obtained by the use of a suppository after the child has sat only a short time on the toilet. Theoretically, one should be able to cure any type of constipation by regulation of the diet alone, but this has not been found to work satisfactorily. Dextrimaltose has been disappointing. Karo has been found more laxative. Malt is mildly laxative. Roughage is not necessary and may even cause damage. Whether the food is cooked or raw makes no apparent difference. I have found agar with oil to be better than oil alone. Buttermilk should be considered a help in the treatment of constipation. Bacillus acidophilus therapy has been of moderate benefit. In constipation during illness only

an enema should be resorted to; no laxative should be given. There is a type of constipation caused by excessive fat, but this is not common at present. Insufficient food must always be checked on. Pylorospasm is a cause of constipation. One must be certain that food is not being retained in the stomach, the quantities passing through being insufficient to give a good stool. A child who has pain with the meals or at the time he is on the stool is likely to become habitually constipated. I have never seen convulsions result from constipation.

DISCUSSION

DR. D. M. DAYTON, Tacoma, Wash.: First of all, the physician must be educated to accept the fact that no harm comes from the child not having a daily movement of the bowel. Then follows the education of the parents. Direct attention must be paid to the intake and not so much to the output. There should be a sufficient amount of vitamin B for muscle tone, and one must rule out any mechanical obstruction. A child having pain should be relieved by dilation.

DR. J. I. DURAND, Seattle: A number of children refuse to have a bowel movement, owing to fear of pain. The underlying cause for the pain and fear should be corrected.

Dr. C. U. Moore, Portland, Ore.: I have in mind the case of a breast-fed baby which has one stool every tenth day. The child is well, but gains only 4 ounces (124.4 Gm.) a week. I believe that petrolagar and mineral oil are not desirable in the treatment of constipation.

ARGYRIA. DR. ARTHUR H. GRAY, Seattle.

A boy, 7 years of age, had been using from 6 to 8 ounces (186.6 to 248.8 Gm.) of argyrol or neosilvol each winter for two years. Owing to the discoloration, his condition was diagnosed as heart disease by the school department, and restriction in exercise was advised. Illness or excitement brings out the color. The hemoglobin content has remained at from 65 to 85 per cent. The color will probably remain permanently.

DISCUSSION

DR. J. I. DURAND, Seattle: I have seen a number of mild cases of this condition. In my experience, the color gradually improves as the child grows older.

ASPIRATION TREATMENT OF EMPYEMA. DR. M. L. BRIDGEMAN, Portland, Ore.

This article will be published in full later.

DISCUSSION

DR. A. H. SPOHN, Vancouver, B. C.: A simple method that I have found effective in this condition is constant suction drainage, a dental dam being applied over the wound and the tube passed into a vacuum bottle.

DR. J. I. DURAND, Seattle: This type of suction drainage was responsible for a rapid cure in a case in which the lungs were not expanding. Within twenty-four hours there was a prompt response in expansion of the lungs and improvement of the general condition and appetite.

DR. FRANK H. DOUGLASS, Seattle: Generally speaking there are three types of treatment for empyema: (1) aspiration, (2) intercostal drainage by tube and (3) resection of the ribs. Aspiration is the method of choice for infants because of its simplicity and the lack of shock. Intercostal drainage is seldom used at present. Resection of the ribs should be resorted to only after all other methods have failed.

DR. ARTHUR H. GRAY, Seattle: Often the pus is too thick for aspiration or intercostal drainage.

DR. E. J. BARNETT, Seattle: In a child over 3 years of age aspiration should be carried out once or twice, and then the patient should be turned over to a surgeon for resection of the ribs.

DR. H. H. SKINNER, Yakima, Wash.: The last patient with empyema whom I treated proved to have lymphosarcoma.

DR. M. L. BRIDGEMAN, Portland, Ore.: In my experience, aspiration has proved successful. Frequent aspiration has been far less objectionable from the standpoint of injury to the patient than the frequent dressings required after resection of the ribs. Regarding pus that is thick, the injection of a small amount of saline solution often results in easier removal of such pus.

MILROY'S DISEASE. DR. J. I. DURAND, Seattle.

A case of Milroy's disease was presented in which enlargement of one leg had been persistent. There was exacerbation accompanied by fever. No cause for the condition was found, and no specific treatment was given.

SYPHILITIC MENINGITIS. DR. W. B. SEELYE, Seattle.

A boy, 2½ years of age, had a condition which was diagnosed as syphilis when he was about 9 months old. The onset was accompanied by frequent convulsions. Spastic paralysis on the right followed. Vision and hearing are satisfactory; mentality is not quite up to par. He has been treated with iodobismitol and sulpharsphenamine, one dose of each being given weekly, with free intervals. Originally the spinal fluid was under increased pressure, was cloudy, contained 1,500 cells and gave a strongly positive Wassermann reaction.

DISCUSSION

DR. M. L. BRIDGEMAN, Portland, Ore.: I should like to mention a case of hydrocephalus in which the condition promptly subsided under antisyphilitic treatment. One case also came to autopsy.

DR. A. REMBE, Seattle: In cases of hydrocephalus one must be sure that the condition is not syphilitic.

DR. D. M. DAYTON, Tacoma, Wash.: From the standpoint of diagnosis, I have found that roentgen rays give positive results more frequently than does serologic examination.

DR. A. REMBE, Seattle: One should qualify that statement; treatment should not be given unless there is symptomatic evidence in addition to roentgenographic evidence.

DR. J. MCGREGOR, Bellingham, Wash.: I have been taking spinal fluid pressure by attaching an apparatus for taking blood pressure.

DR. N. W. CLEIN, Seattle: Roentgenograms often give positive results when the Wassermann reaction is negative. I should like to mention treatment with acetarsone.

DR. E. J. BARNETT, Seattle: Good results are obtained in infants with stovarsol but not in the older child. In the case demonstrated, one should consider the possibility of juvenile dementia paralytica. The child has a happy, overgenial expression that should make one suspicious. If that is the case, malarial treatment should be used.

DR. M. L. BRIDGEMAN, Portland, Ore.: Treatment with stovarsol is satisfactory, but this preparation is no less expensive than iodobismitol and sulpharsphenamine.

DR. R. H. SOMERS, Seattle: This case is particularly interesting because when the child was first seen he was in a semicoma, with cloudy spinal fluid and a high cell count. Feeding by tube was necessary for fifty-two hours. Under the circumstances, recovery was a little unusual. From the appearance of the child, one should certainly consider the possibility of juvenile dementia paralytica.

STAPHYLOCOCCUS TOXOID. DR. A. H. SPOHN, Vancouver, B. C.

This article will be published in full later.

DISCUSSION

DR. R. P. KINSMAN, Vancouver, B. C.: My experience agrees with that of Dr. Spohn that staphylococcus toxoid is the best means of treating chronic staphylococcic infections, giving results that nothing else gives.

DR. E. D. CARDER, Vancouver, B. C.: My experience is not so extensive as that of Dr. Spohn and Dr. Kinsman, but the results obtained so far agree with theirs. Staphylococcus toxoid seems to be the treatment of choice in staphylococcic infection, but it must be proved that the infection is definitely staphylococcic.

VITAMIN D MILK. DR. V. W. SPICKARD, Seattle.

Two methods of supplying the public with vitamin D milk seem to be in favor: feeding the cow irradiated yeast and irradiating the milk directly. In this vicinity both methods are used. Data on the relative values of the various forms of vitamin D apparently show that the vitamin D derived from milk directly irradiated is of higher value. It is advised that the advertising of the milk companies be carefully controlled, and that the product be subjected to biologic analysis at regular intervals.

DISCUSSION

DR. W. D. TODD, Portland, Ore.: Whether vitamin D milk is to become valuable to the medical profession depends to some extent on rigid control of its potency. There is but one method of control, and that is by bio-assay. As the Wisconsin Alumnae Research Foundation is sponsoring two of the methods of producing vitamin D milk, it is logical to expect that institution to take an active part in the control of the potency. The price of such milk should be kept within reach of the average family. It has been stated that 50 units of vitamin D in a quart (946.3 cc.) of irradiated milk is equivalent to 200 or 250 units in cod liver oil or to 800 units in viosterol. Pasteurization of the milk may be done before or after contact with the ultraviolet rays.

DR. C. U. MOORE, Portland, Ore.: Seattle is the first city on the west coast to produce vitamin D milk. It is difficult to give enough cod liver oil to prevent rickets. The responsibility of this procedure rests on the physicians, and the state board of health should have some control over the vitamin D content of such milk.

DR. N. W. CLEIN, Seattle: When is this vitamin proposition going to end? In Seattle we have milk, bread and sausage containing vitamin D.

DR. C. LUVERNE SMITH, Seattle: Why does the Wisconsin Alumnae Research Foundation have so many grants?

DR. A. H. SPOHN, Vancouver, B. C.: Is irradiated milk cheaper than yeast milk?

DR. W. D. TODD, Portland, Ore.: The cost of producing this milk is less than that of producing yeast milk.

DR. F. R. FISCHER, Spokane, Wash.: Is there any connection between the machine manufactured and the Wisconsin Alumnae Research Foundation?

DR. W. D. TODD, Portland, Ore.: No.

DR. E. J. BARNETT, Seattle: Does boiling interfere with the vitamin D? Will this milk cure rickets?

DR. W. D. TODD, Portland, Ore.: Boiling does not interfere with the vitamin D. If given in sufficient quantities, the milk will prevent rickets and will cure it to some degree.

DR. A. REMBE, Seattle: This should be a good product, if produced satisfactorily.

DR. R. P. KINSMAN, Vancouver, B. C.: Is all the vitamin D in the cream?

DR. W. D. TODD, Portland, Ore.: Skim milk cannot be activated.

DR. M. G. EVANS, Portland, Ore.: Can physicians control the irradiation of milk and the price?

DR. W. D. TODD, Portland, Ore.: Physicians can control the efficiency of the product, but it is difficult to control its price.

DR. C. U. MOORE, Portland, Ore.: Are we going to lead or follow in this project?

DR. A. H. SPOHN, Vancouver, B. C.: It is not possible for the average person to ingest a quart of milk daily.

DR. W. D. TODD, Portland, Ore.: Twenty-four ounces (746.4 Gm.) of milk containing 50 units should be a sufficient prophylactic.

DR. V. W. SPICKARD, Seattle: I do not approve of the patent idea of the Wisconsin Alumnae Research Foundation. It would seem better for more than one dairy to produce this product. It should be well controlled by the health department by bio-assays. There is little doubt as to its efficacy in the prevention and cure of rickets. Advertising matter should not contain too extravagant claims. Small babies cannot take enough milk to prevent rickets.

# Book Reviews

**Protection of Motherhood and Childhood in the Soviet Union.** By E. Conus. Pp. 117. Moscow: State Medical Editorship, 1933.

This official publication describes the attitude taken by the Soviet Union toward women and children and the practical methods employed in their education, protection and work. The following titles of chapters illustrate the contents of the book: I, Women and Children in Prerevolutionary Russia; II, The Family and Marriage in the U.S.S.R.; III, Woman in Economic and Social Life; IV, Medical Assistance for Women; V, Crèches; VI, Consultations for Children; VII, Preschool Institutions; VIII, School, and IX, Research Work and the Training of Personnel.

For details of the Soviet plan for the protection of women and children the original article should be read.

**Les prématurés.** By H. Vignes and G. Blechmann. Price, 20 francs. Pp. 159, with 40 figures. Paris: Masson & Cie, 1933.

This small volume contains the lectures delivered by Vignes and Blechmann at the Maternité de la Charité. The first part, by Vignes, deals with the physiology of the premature infant and includes a description of the prenatal and postnatal growth of the body and the various internal organs, chemical analyses and studies on digestion, the regulation of temperature and respiration. The second part, by Blechmann, covers the clinical considerations involved in the care of premature infants, such as general hygiene, feeding and common disorders and their treatment. The treatise is based on sound scientific principles and is concise and interesting. It is recommended for physicians dealing with premature infants.

**Scritti di pediatria.** By Carlo Francioni. Price, 120 lire. Pp. 1,014. Bologna: L. Cappelli, 1933.

This book of 1,014 pages contains contributions to the literature of the eminent Italian pediatrician, Prof. Carlo Francioni. The articles are arranged not according to the time of appearance but according to subjects. It is interesting to note the wide range of articles. Nutrition, nervous diseases, various internal diseases, constitutional defects and many other subjects receive authoritative attention from the pen of this master.

**Rapport sur le Service des Enfants Assistés du Département de la Seine. Part I: Compte Moral et Administratif.** Pp. 157, with 17 tables. Paris: Montévrain, 1933.

This report, which is published yearly, is a comprehensive account of the work done by this public health organization of the French government. It is divided into several chapters detailing the work along certain lines. A number of tables demonstrating various points in the text appear at the end.

# Directory of Pediatric Societies *

## INTERNATIONAL

### International Association of Preventive Pediatrics

President: Professor Taillens, Lausanne, Switzerland.
Secretary: Dr. P. Oltramare, rue Decandolle, Geneva, Switzerland.

## FOREIGN

### Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. Leonard G. Parsons, 58, Calthorpe Road, Birmingham, England.
Secretary: Dr. W. G. Wyllie, 33, Wimpole St., W. 1, London.

## NATIONAL

### American Medical Association, Scientific Assembly, Section on Diseases of Children

Chairman: Dr. Alfred A. Walker, Highland Plaza Apartments, Birmingham, Ala.
Secretary: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.

### American Academy of Pediatrics

President: Dr. John Ruhräh, 11 E. Chase St., Baltimore.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.

### American Child Health Association

President: Dr. Samuel McC. Hamill, 1822 Spruce St., Philadelphia.
Secretary: Dr. Philip Van Ingen, 125 E. 71st., New York.

### American Hospital Association, Children's Hospital Section

President: Mr. Robert Witham, Children's Hospital, Denver.
Secretary: Miss Agnes O'Roke, Kosair Crippled Children's Hospital, Louisville, Ky.
Place: Philadelphia. Time: Sept. 24-28, 1934.

### American Pediatric Society

President: Dr. Borden S. Veeder, 3720 Washington Ave., St. Louis.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.

### Canadian Society for the Study of Diseases of Children

President: Dr. D. P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary-Treasurer: Dr. R. R. Struthers, 1414 Drummond St., Montreal.
Place: Buffalo, N. Y. Time: June 1935.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

### Society of Pediatric Research

President: Dr. Rustin McIntosh, College of Physicians and Surgeons, Columbia University, New York.
Secretary-Treasurer: Dr. Charles F. McKhann, Harvard Medical School, Boston.

## SECTIONAL

### North Pacific Pediatric Society

President: Dr. Arthur H. Gray, 1117 Second Ave., Seattle.
Secretary: Dr. Raymond H. Somers, Cobb Bldg., Seattle.

### Southern Medical Association, Section on Pediatrics

Chairman: Dr. Hugh L. Dwyer, 406 W. 34th St., Kansas City, Mo.
Secretary: Dr. Luther W. Holloway, 117 W. Duval St., Jacksonville, Fla.

## STATE

### Alabama Pediatric Society

President: Dr. C. E. R. Parker, 401 S. Court St., Montgomery.
Secretary-Treasurer: Dr. John W. Simpson, 1117 S. 22d St., Birmingham.

### Georgia Pediatric Society

President: Dr. Joseph Yampolsky, 311 Doctors Bldg., Atlanta.
Secretary-Treasurer: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.

### Louisiana State Pediatric Society

President: Dr. John Signorelli, Louisiana State University Medical School, New Orleans.
Secretary-Treasurer: Dr. Edwin A. Socola, Louisiana State University Medical School, New Orleans.
Place: New Orleans. Time: April, 1935.

### Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Adolph G. De Sanctis, 12 E. 11th St., New York.
Secretary: Dr. George M. Retan, 459 James St., Syracuse.

### Michigan State Medical Society, Pediatric Section

Chairman: Dr. W. A. Collins, 103 W. Burdick St., Kalamazoo.
Secretary: Dr. Edgar E. Martmer, 749 David Whitney Bldg., Detroit.
Place: Battle Creek. Time: September, 1934.

### Mississippi State Pediatric Society

President: Dr. N. C. Womack, Jackson Infirmary, Jackson.
Secretary-Treasurer: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Place: To be designated by Society. Time: Yearly.

### Nebraska Pediatric Society

President: Dr. W. O. Colburn, 725 Sharp Bldg., Lincoln.
Secretary-Treasurer: Dr. C. G. Weigand, 1614 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Second Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

### North Carolina Pediatric Society

President: Dr. J. Buren Sidbury, 15 N. Fifth St., Wilmington.
Secretary: Dr. E. K. McLean, 121 W. Seventh St., Charlotte.
Place: Various children's hospitals. Time: Twice a year.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Clark H. Hall, 117 N. Broadway, Oklahoma City.
Secretary: Dr. M. J. Searle, 108 W. 16th St., Tulsa.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Julian P. Price, Medical Bldg., Florence.
Secretary-Treasurer: Dr. Leland B. Salters, 317 S. Warley Ave., Florence.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Owen H. Wilson, 706 Church St., Nashville.
Secretary: Dr. Joe T. Smith, 702 Medical Arts Bldg., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. Sidney R. Kaliski, Moore Bldg., San Antonio.
Secretary-Treasurer: Dr. Frank M. Martin, 321 Medical Arts Bldg., San Antonio.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Thomas D. Jones, Medical Arts Bldg., Second and Franklin Streets, Richmond.
Secretary: Dr. W. A. McGee, 2618 Grove Ave., Richmond.
Place: Alexandria. Time: October, 1934.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. R. C. Hood, 428 W. Pike St., Clarksburg.
Secretary: Dr. Russell C. Bond, 1325 Chapline St., Wheeling.

## LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. A. Garvin, Carnegie Medical Bldg., Cleveland.
Secretary: Dr. William M. Champion, 2323 Prospect Ave., Cleveland.
Place: 2009 Adelbert Road. Time: Four meetings, from September to May.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. Gladys Boyd, 56 DeLisle St., Toronto.
Secretary: Dr. Lawrence Murray, 1870 Bloor St., W., Toronto.

BRONX PEDIATRIC SOCIETY

President: Dr. Morris Gleich, 9 Post Ave., New York.
Secretary: Dr. Harry D. Pasachoff, 1560 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Last Wednesday of each month, except June, July and August.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Fourth Thursday of October, January and April.

### Chicago Pediatric Society

President: Dr. Charles Schott, 48 W. Division St., Chicago.
Secretary: Dr. Bert I. Beverly, 8 S. Michigan Ave., Chicago.
Place: City Club. Time: Third Tuesday of each month.

### Dallas County Pediatric Society

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas, Texas.
Secretary: Dr. R. S. Usry, 1835 Garrett Ave., Dallas, Texas.
Place: Bradford Memorial Hospital. Time: 1 p. m., first and third Saturdays of each month.

### Detroit Pediatric Society

President: Dr. John A. Johnston, 2799 W. Grand Blvd., Detroit.
Secretary: Dr. Edgar E. Martmer, 749 David Whitney Bldg., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month.

### Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. L. H. Muse, 384 Peachtree St., Atlanta.
Secretary: Dr. T. I. Willingham, 384 Peachtree St., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

### Houston Pediatric Society

President: Dr. Frank Lancaster, Medical Arts Bldg., Houston, Texas.
Secretary-Treasurer: Dr. A. A. Little, Jr., 817 Holman Ave., Houston, Texas.
Time: Third Monday of each month.

### Intermountain Pediatric Society

President: Dr. Helmina Jeidell, 11 Exchange Pl., Salt Lake City, Utah.
Secretary-Treasurer: Dr. Edwin R. Murphy, 9 Exchange Pl., Salt Lake City, Utah.
Place: Salt Lake City, General Hospital. Time: First Thursday of each month, 8 p. m.

### Kansas City (Missouri) Pediatric Society

President: Dr. Hugh L. Dwyer, 406 W. 34th St., Kansas City.
Secretary: Dr. John Aull, 906 Grand Ave., Kansas City.

### Memphis Pediatric Society

President: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Clyde V. Croswell, 1052 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month.

### Milwaukee Pediatric Society

President: Dr. F. R. Janney, 1411 Wauwatosa Ave., Wauwatosa, Wis.
Secretary: Dr. John H. Reynolds, 1628 Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

### New England Pediatric Society

President: Dr. James L. Gamble, 33 Edgehill Road, Brookline, Mass.
Secretary: Dr. Gerald Hoeffel, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

### New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Martha Wollstein, Babies' Hospital of City of New York, New York.
Secretary: Dr. Harry Bakwin, 132 E. 71st St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

### Northwestern Pediatric Society

President: Dr. Alexander Stewart, 459 Lowry Medical Arts Bldg., St. Paul.
Secretary: Dr. E. F. Robb, 1801 Lyndale Ave., S. Minneapolis.

### Philadelphia Pediatric Society

President: Dr. John D. Donnelly, 115 Bryn Mawr Ave., Bala, Pa.
Secretary: Dr. James E. Bowman, 4091 Comly St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to June, inclusive.

### Pittsburgh Pediatric Society

President: Dr. Henry C. Flood, 119 S. Highland Ave., Pittsburgh.
Secretary: Dr. E. R. McCluskey, Highland Bldg., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to April, inclusive.

### Richmond Pediatric Society

President: Dr. W. A. McGee, 2618 Grove Ave., Richmond, Va.
Secretary-Treasurer: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: First Thursday of each month (except July, August and September).

### Rochester Pediatric Society

President: Dr. H. F. Rowley, 176 S. Goodman St., Rochester, N. Y.
Secretary: Dr. J. M. Parker, 26 S. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month from October to May.

### Rocky Mountain Pediatric Society

President: Dr. Arthur L. Esserman, Republic Bldg., Denver.
Secretary: Dr. Ralph Verploeg, 19th and Gilpin Sts., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7 p. m.

### St. Louis Pediatric Society

President: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Katherine Bain, Beaumont Bldg., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

### Seattle Pediatric Society

President: Dr. Armin C. Rembe, 1215 4th Ave., Seattle.
Secretary: Dr. Frank H. Douglass, Medical-Dental Bldg., Seattle.
Place, College Club. Time. Third Friday of each month, 7 p. m.

### Southwestern Pediatric Society

President: Dr. James E. Harvey, 60 S. Lake Ave., Pasadena, Calif.
Secretary: Dr. E. Earl Moody, 3780 Wilshire Blvd., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

### University of Michigan Pediatric and Infectious Disease Society

President: Dr. John F. Sanders, 320 Townsend St., Lansing, Mich.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Place: University Hospital, Ann Arbor, Mich. Time: Nov. 23-24, 1934.

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